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(54) Title: **METHOD FOR RAPID SCREENING OF BACTERIAL TRANSFORMANTS AND NOVEL SIMIAN ADENOVIRUS PROTEINS**

(57) Abstract: Chimpanzee serotype C68 proteins, peptides, and polypeptide are provided. Also provided are novel adenoviruses derived from these proteins, as well as compositions containing these proteins and methods of using same for immunization and therapy. Further, a rapid method for screening recombinant transformants using a visually detectable method is described.



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## METHOD FOR RAPID SCREENING OF BACTERIAL TRANSFORMANTS AND NOVEL SIMIAN ADENOVIRUS PROTEINS

### BACKGROUND OF THE INVENTION

5                   Recombinant adenoviruses have been described for gene therapy and vaccine uses.

                  Adenoviruses have a characteristic morphology with an icosahedral capsid consisting of three major proteins, hexon (II), penton base (III) and a knobbed fibre (IV), along with a number of other minor proteins, VI, VIII, IX, IIIa and IVa2 [W.C. Russell, *J. Gen Virol.*, 81:2573-2604 (Nov 2000)]. The virus genome is a linear, double-stranded DNA  
10                   with a terminal protein attached covalently to the 5' termini, which have inverted terminal repeats (ITRs). The virus DNA is intimately associated with the highly basic protein VII and a small peptide termed *mu*. Another protein, V, is packaged with this DNA-protein complex and provides a structural link to the capsid via protein VI. The virus also contains a virus-  
15                   encoded protease, which is necessary for processing of some of the structural proteins to produce mature infectious virus.

                  There continues to be a need for recombinant viral vectors and improved methods for making these vectors.

### 20                   SUMMARY OF THE INVENTION

                  In one aspect, the invention provides a method for rapid screening of bacterial transformants. The method involves engineering a recombinant shuttle vector comprising a nucleic acid cassette containing a transgene and a nucleic acid sequence encoding prokaryotic green fluorescent protein (GFP) operably linked to regulatory sequences which permit its  
25                   expression in a host cell. Thereafter, host cells are transfected with the shuttle vector and screened for expression of GFP. The absence of green color (i.e., white) is indicative of a cell carrying the recombinant virus. Expression of GFP is readily detected by the green color when activated by fluorescent light, and indicates the presence of parent virus (i.e., absence of recombinant).

In another aspect, the invention provides capsid proteins of C68, isolated from other C68 proteins, and characterized by the amino acids provided herein.

In still another embodiment, the invention provides adenoviral vectors and non-viral targeting proteins derived from the C68 capsid proteins, termed herein C68-derived  
5 constructs.

Yet other advantages of the present invention will be readily apparent from the following detailed description of the invention.

### Brief Description of the Drawings

10 Fig. 1 summarizes the genetic organization of the chimpanzee adenovirus C68 genome. In Fig. 1A the genome of the C68 chimpanzee adenovirus is schematically represented by the box at the top. The inverted terminal repeats are shaded black and the early regions are shaded gray. The arrowheads above the box indicate the direction of expression of the early genes. The line below the box represents the division of the genome  
15 into 100 map units. The arrows below the line represent the five late gene regions and the proteins encoded in each region. The numbers below the box or arrows indicate the start (promoter or initiation codon) and end (canonical PolyA signal) for each region. \* represents the E2A late promoter. Fig. 1B illustrates the PstI clones; Fig. 1C illustrates the BamHI clones. Fig. 1D illustrates the HindIII clones. For parts 1B-1D, the unshaded regions indicate  
20 that a fragment was cloned into a plasmid vector, while the shaded regions indicate that the restriction fragment was not cloned. For each section the fragment name, alphabetical with A being the largest fragment, and the fragment size are listed above the box and the fragment end points are listed below the box.

Fig. 2 provides a sequence alignment of the C68 hexon protein [aa 131 to 441 of SEQ  
25 ID NO:16] with Ad4 [SEQ ID NO:34], Ad16 [SEQ ID NO:35], Ad3 [SEQ ID NO:36], Ad7 [SEQ ID NO:37], and Ad2 [SEQ ID NO:38]. The deduced amino acid sequences of highly similar human adenovirus hexons were compared with the C68 chimpanzee adenovirus using CLUSTAL X. Serotypes and subgroups are indicated on the left margin, followed by the residue number. The numbering refers to the amino acid position with respect to the start of  
30 translation. Amino acids are shaded with respect to C68 to highlight sequence similarities

(gray) and identities (black). The seven hypervariable regions within loop domains DE1 and FG1 are labeled along the bottom and correspond to the following Ad2 sequences in the alignment: HVR1, 137-188; HVR2, 194-204; HVR3, 222-229; HVR4, 258-271; HVR5, 278-294; HVR6, 316-327; and HVR7, 433-465 of SEQ ID NO:16. The GenBank accession numbers for the sequences shown are as follow: AAD03657 (Ad4), S37216 (Ad16), S39298 (Ad3), AAD03663 (Ad7), and NP040525 (Ad2).

Fig. 3 provides an alignment of the amino acid sequences of the fiber knob domains of chimpanzee C68 (Pan-9) [amino acids 247 to 425 of SEQ ID NO: 27] and the human adenovirus serotypes 2 [SEQ ID NO: 39] and 5[SEQ ID NO:40].

Fig. 4 provides an alignment of the amino acid sequences of the L1 and a portion of the L2 loops of the capsid hexon on the human adenovirus serotype 5 [SEQ ID NO:41] and chimpanzee C68 (Pan-9) [amino acids 125 to 443 of SEQ ID NO:16] adenovirus sequences. The intervening conserved region is part of the pedestal domain conserved between adenovirus serotypes.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel adenovirus capsid proteins derived from the unique sequences of chimpanzee adenovirus C68. The capsid proteins of the invention are useful for a variety of purposes, including non-viral targeted delivery to cells and for creating recombinant viral vectors. These proteins and viral vectors are useful for delivery of heterologous molecules to target cells.

The invention further provides a novel method for rapid screening of bacterial transformants obtained during production of the novel adenoviral capsids of the invention, and during production of a variety of other viral or non-viral constructs. In this method, at least the shuttle vector is engineered to contain a marker gene, e.g., green fluorescent protein (GFP), gene under the control of a suitable promoter. The transformed cells are screened for expression of marker. In the case of GFP, white colonies are recombinants while green colonies are residual parental plasmid.

## I. Novel Adenovirus Capsid Proteins

In one aspect, the invention provides unique C68 adenoviral capsid proteins, including the C68 hexon region, the C68 penton region, and the C68 fiber region, and fragments thereof. Suitably, these capsid proteins can be substantially pure, i.e., are free of other proteins. Preferably, these proteins are at least 10% homogeneous, more preferably 60% homogeneous, and most preferably 95% homogeneous.

In addition, the invention provides unique C68-derived capsid proteins. As used herein, a C68-derived capsid protein includes any C68 capsid protein or a fragment thereof including, without limitation, a polypeptide, peptide or a consecutive sequence of at least 8 amino acid residues unique to a C68 capsid protein and which is free of other proteins. A C68-derived capsid protein also includes a capsid protein that contains a C68 capsid protein or fragment thereof as defined above, including, without limitation, a chimeric capsid protein, a fusion protein, an artificial capsid protein, a synthetic capsid protein, and a recombinant capsid proteins, without limitation to means of generating these proteins. Suitably, these C68-derived capsid proteins contain one or more C68 regions or fragments thereof (e.g., a hexon) in combination with capsid regions or fragments thereof of different adenoviral serotypes, or of non-adenoviral sources, as described herein. These C68-derived capsid proteins may be used in non-viral targeting of useful molecules to cells, or for production of viral vectors, as described herein.

A "modification of a capsid protein associated with altered tropism" as used herein includes an altered capsid protein, i.e, a penton, hexon or fiber protein region, or fragment thereof, such as the knob domain of the fiber region, or a polynucleotide encoding same, such that specificity is altered.

In one embodiment, the amino acid sequences of the C68 penton protein are provided

in SEQ ID NO:12: MMRRAYPEGPPPSYESVMQQAMAAAAMQPPLEAPYVPPRYLAPT  
EGRNSIRYSELAPLYDTTRLYLVDNKSADIASLNYQNDHSNFLTTVVQNNDFTPTEAS  
TQTINFDESRWGGQLKTIMHTNMPNVNEFMYSNKFARVMVSRKTPNGVTVTEDYDG  
SQDELKYEWVEFELPEGNFSVTMTIDLNNAIIDNYLAVGRQNGVLES DIGVKFDTRN  
FRLGWDPVTELVMPGVYTNEAFHPDIVLLPGCGVDFTESRLSNLLGIRKRQPFQEGFQ  
IMYEDLEGGNIPALLDVDAYEKSKEAATAAVATASTEVRGDNFASAAVAAAEA  
AETESKIVIQPVEKDSKNRSYNVLPDKINTAYRSWYLAYNYGDPEKGVRSWTLTTS

VTCGVEQVYWSLPDMMQDPVTFRSTRQVSNPVVGAE LLPVYSKSFNEQAVYSQQLR  
 AFTSLTHVFNRFENQILVRPPAPTITTVSENPALTDHGTLPLRSSIRGVQRVTVTD  
 ARRRTCPIVYKALGIVAPRVLSSRTF.

Suitably, this penton protein, or unique fragments thereof, may be utilized for a  
 5 variety of purposes. Examples of suitable fragments include the C68 penton having N-  
 terminal and/or C-terminal truncations of about 50, 100, 150, or 200 amino acids, based upon  
 the amino acid numbering provided above and in SEQ ID NO:12. Other suitable fragments  
 include shorter internal, C-terminal, or N-terminal fragments. Further, the penton protein  
 may be modified for a variety of purposes known to those of skill in the art.

10 The sequences of the C68 hexon are provided in SEQ ID NO:16:

MATPSMLPQWAYMHIAGQDASEYLSPLGVQFARATDTYFSLGNK  
 FRNPTVAPTHDVTDRSQRLTLRFVPVDREDNTYSYKVRVTLAVGDNRVLDMASTYFD  
 15 IRGVLDRGSPFKPYSGTAYNSLAPKGAPNTCQWTYKADGETATEKTYTYGNAPVQGIN  
 ITKDGILGTDTDQPIYADKTYQPEPQVGDAEWHDTGTDEKYGGRALKPDTKMKPC  
 20 YGSFAKPTNKEGGQANVKTGTGTTKEYDIDMAFFDNRSAAAAGLAPEIVLYTENVLDLE  
 TPDTHIVYKAGTDDSSSSINLGQQAMPNRPNIIGFRDNFIGLMYYNSTGNMGVLAGQA  
 25 SQLNAVVDLQDRNTELSYQLLLDSLGRTRYFSMWNQAVDSYDPDVRIENHGVDEL  
 PNYCFPLDAVGRTDTYQGIKANGTDQTTWTKDDSVNDANEIGKGNPFAMEINIQANLW  
 RNFLYANVALYLPDSYKYTPANVTLPNTNTYDYMNGRVVAPSLVDSYINIGARWSLD  
 30 PMDNVNPFNHHRNAGLRYRSMLLGNRGYVPFHIQVPQKFFAIKSLLLPGSYTYEWNF  
 RKDVNMILQSSLGNDLRTDGASISFTSINLYATFFPMAHNTASTLEAMLRNDTNDQSF  
 NDYLSAANMLYPIPANATNPISIPSRNWA AFRGWSFTRLKTETPSLGSFGDPYFVY  
 35 SGSIPYLDGTFYLNHTFKKVSITFDSSVSWPGNDRLLTPNEFEIKRTVDGEGYNVAQC  
 NMTKDWFLVQMLAHYNIGYQGFYVPEGYKDRMYSFFRNFPMSRQVVDEVNYKDYQAV  
 40 TLAYQHNNSGFVGYLAPTMRQQPYXPAXYPYPLIGKSAVTSVTQKKFLCDRVMWRI PF  
 SSNFMSMGALTDLGQNMLYANSAHALDMNFEVDPMDESTLLYVVFVFDVVRVHQPHR  
 GVIEAVYXRTPFSAGNATT.

45 Suitably, this hexon protein, or unique fragments thereof, may be utilized for a variety  
 of purposes. Examples of suitable fragments include the C68 hexon having N-terminal  
 and/or C-terminal truncations of about 50, 100, 150, 200, 300, 400, or 500 amino acids, based  
 upon the amino acid numbering provided above and in SEQ ID NO:16. Other suitable

fragments include shorter internal, C-terminal, or N-terminal fragments. For example, one suitable fragment the loop region (domain) of the hexon protein, designated DE1 and FG1, or a hypervariable region thereof. Such fragments include the regions spanning amino acid residues about 125 to 443; about 138 to 441, or smaller fragments, such as those spanning  
 5 about residue 138 to residue 163; about 170 to about 176; about 195 to about 203; about 233 to about 246; about 253 to about 264; about 287 to about 297; and about 404 to about 430 of C68, with reference to SEQ ID NO:16. Other suitable fragments may be readily identified by one of skill in the art. Further, the hexon protein may be modified for a variety of purposes known to those of skill in the art.

10 In one example, it may be desirable to generate an adenovirus having an altered hexon protein utilizing the C68 hexon protein sequences of the invention. One suitable method for altering hexon proteins is described in US Patent 5,922,315, which is incorporated by reference. In this method, at least one loop region of the adenovirus hexon is changed with at least one loop region of another adenovirus serotype. Thus, at least one loop region of such  
 15 an altered adenovirus hexon protein is a C68 hexon loop region. In one embodiment, a loop region of the C68 hexon protein is replaced by a loop region from another adenovirus serotype. In another embodiment, the loop region of the C68 hexon is used to replace a loop region from another adenovirus serotype. Suitable adenovirus serotypes may be readily selected from among human and non-human serotypes, as described herein. Where non-  
 20 human adenoviruses are selected, the serotypes are preferably selected from non-human primates. However, the selection of a suitable serotype is not a limitation of the present invention. Still other uses for the C68 hexon protein sequences of the invention will be readily apparent to those of skill in the art.

The sequences of the C68 fiber protein are: SEQ ID NO:27:

25 MSKKRVRVDDDFDPVYPYDADNAPTVPFINPPFVSSDGFQEKPL  
 GVLSRLRLADPVTTKNGEITLKLGEVDLDSSGKLISNTATKAAAPLSFSNNTISLNMD  
 PFYTKDGKLSLQVSPPLNILRTSILNTLALGFGSGLGLRGSALAVQLVSPLTFD TDGN  
 IKLTLDRLHVTTGDAIESNISWAKGLKFEDGAIATNIGNGLEFGSSSTETGVDDAY  
 30 PIQVKLGSGLSFDSTGAIMAGNKEDDKLTLTWTPDPSPNCQILAENDAKLTLCLTKCG  
 SQILATVSVLVVSGNLNPITGTVSSAQVFLRFDANGVLLTEHSTLKKYWG YRQGDSI  
 DGTPTYNAVGFMPNLKAYPKSQSSTTKNNIVGQVYMNGDVSKPMLLTITLNGTDDSNS  
 TYSMSFSYTWNGSYVGATFGANSYTF SYIAQE.

Suitably, this fiber protein, or unique fragments thereof, may be utilized for a variety of purposes. One suitable fragment is the fiber knob, which spans about amino acids 247 to 425 of SEQ ID NO: 27. Examples of other suitable fragments include the C68 fiber having N-terminal and/or C-terminal truncations of about 50, 100, 150, or 200 amino acids, based upon the amino acid numbering provided above and in SEQ ID NO:27. Still other suitable fragments include internal fragments. Further, the fiber protein may be modified using a variety of techniques known to those of skill in the art.

The amino acid sequences of other useful gene products of C68 are provided in SEQ ID Nos. 1 – 11, 13 – 15, 17 – 26, and 28 -38 of the attached sequence listing. More particularly, these sequences are as follows.

Regions		Ad C68 – CDS, With ref to SEQ ID NO:33.	Ad C68 SEQ ID NO:
E1a	11kDa	578... 649, 1236 ... 1469	1
	28.2 kDa	578 ... 1142, 1236 ... 1444	2
	24.8 kDa	578... 1049, 1236 ... 1444	3
E1b	20.5kDa	1603 ... 2163	4
	54.7 kDa	1908 ... 3404	5
	18.5 kDa	1908 ... 2200, 3188 ... 3404	6
	10.1 kDa	1908 ... 2170, 3306 ... 3324	7
IX	Hexon-associated protein – pIX	3489 ... 3917	8
IVa2	Maturation protein – pIVa2	Complement (3976 ... 5309, 5588 ... 5600)	9
L1	21.9kDa	7858 ... 8460	10
	42.9 kDa	10825 ... 12000	11
L2	Penton – pIII	13888 ... 15492	12
	Major core protein – pVIII	15493 ... 16098	13
	Minor Core Protein – pV	16120 ... 17190	14
L3	Hexon-associated protein – pVI	17442 ... 18215	15
	Hexon – pII	18322 ... 21123	16
E2a	DNA-Binding Protein Endopeptidase	Complement (21835 ... 23376)	17
L4	Virion morphogenesis-associated protein 24.3 kDa	Complement (25529 ... 25862, 26032 ... 26366)	18
	Hexon-associated protein - pVIII	26446 ... 27129	19



Regions		Ad C68 – CDS, With ref to SEQ ID NO:33.	SEQ ID NO:
E3	11.6 kDa	27130 ... 27450	20
	16 kDa	(27404 ... 27477, 27666 ... 28032)	21
	19.3 kDa	28014 ... 28544	22
	22.3	28572 ... 29186	23
	9.9 kDa	30722 ... 30997	24
	15.6 kDa	31003 ... 31434	25
	14.7 kDa	31427 ... 31834	26
L5	Fiber - pIV	32137 ... 33414	27
E4	ORF7-like protein	Complement (33521 ... >33772)	28
	Orf 6 – 33 kDa	Complement (33769 ... 34674)	29
	Orf4 – 13.2 kDa	Complement (34580 ... 34945)	30
	Orf 3 – 12. 8 kDa	Complement (34955 ... 35308)	31
	Orf 2 – 14.2 kDa	Complement (35305 ... 35694)	32

Thus, the invention provides unique C68 proteins, peptides and fragments thereof, which are produced recombinantly or by other methods. Suitably, such fragments are at least 8 amino acids in length. However, fragments of other desired lengths are readily utilized. In addition, the invention encompasses such modifications as may be introduced to enhance yield and/or expression of a C68 protein or fragment, construction of a fusion molecule in which all or a fragment of the C68 protein or fragment is fused (either directly or via a linker) with a fusion partner to enhance. Other suitable modifications include, without limitation, truncation of a coding region (e.g., a protein or enzyme) to eliminate a pre- or pro-protein ordinarily cleaved to produce the mature protein or enzyme and/or mutation of a coding region to provide a secretable gene product. Still other modifications will be readily apparent to one of skill in the art. The invention further encompasses proteins having at least about 95% to 99% identity to the C68 proteins provided herein.

The term “substantial homology” or “substantial similarity,” when referring to a protein or fragment thereof, indicates that, when optimally aligned with appropriate amino acid insertions or deletions with another protein, there is nucleotide sequence identity in at least about 95 to 99% of the aligned sequences .

The term “percent sequence identity” or “identical” in the context of proteins or fragments thereof refers to the amino acids in the two sequences that are the same when

aligned for maximum correspondence. The length of sequence identity comparison may be over the full length of a protein, enzyme, polypeptide, peptide, or other fragment of at least about 200 to 500 amino acids, is desired. However, identity among smaller fragments, e.g. of at least about 8 amino acids, usually at least about 20 to 24 amino acids, at least about 28 to 32 amino acids, at least about 50 or more amino acids, may also be desired.

Identity is readily determined by one of skill in the art by resort to algorithms and computer programs known by those of skill in the art. As described herein, alignments are performed using any of a variety of publicly or commercially available Multiple Sequence Alignment Programs, such as "Clustal W", accessible through Web Servers on the internet.

Alternatively, Vector NTI utilities are also used. There are also a number of algorithms known in the art that can be used to measure amino acid sequence identity, including those contained in the programs described above. Generally, these programs are used at default settings, although one of skill in the art can alter these settings as needed. Alternatively, one of skill in the art can utilize another algorithm or computer program that provides at least the level of identity or alignment as that provided by the referenced algorithms and programs.

As described herein, the C68-derived capsid proteins of the invention are particularly well suited for use in applications in which the neutralizing antibodies diminish the effectiveness of other Ad serotype based targeting proteins and vectors, as well as other viral vectors. The C68-derived constructs of the invention are particularly advantageous in readministration for repeat gene therapy or for boosting immune response (vaccine titers).

Also provided by the present invention are artificial adenoviral capsid proteins, which involve modifications and chimeric capsids constructed using the C68 adenoviral capsid proteins of the invention. Such artificial capsid proteins can be constructed using the amino acid sequences of the chimp C68 Ad hexon of the invention. Because the hexon protein is the determinant for serotype of an adenovirus, such artificial hexon proteins would result in adenoviruses having artificial serotypes. Other artificial capsid proteins can also be constructed using the chimp Ad penton sequences and/or fiber sequences of the invention and/or fragments thereof.

In one embodiment, a chimeric C68 capsid is constructed using C68 hexon and C68 fiber and a penton from another adenovirus. Alternatively, a chimeric C68 capsid comprises

a C68 hexon and a fiber and penton from one or more different adenoviruses. Another chimeric adenovirus capsid comprises the C68 fiber and a penton and a hexon from one or more different different adenovirus serotypes. Yet another chimeric adenovirus capsid comprises the C68 penton and a fiber and hexon from one or more different adenovirus serotypes. Suitably, for such chimeric and artificial capsids constructed from C68 proteins, the non-C68 adenovirus components may be readily selected from other adenovirus serotypes.

Under certain circumstances, it may be desirable to use one or more of the C68-derived capsid proteins or a fragment thereof to generate an antibody. The term "an antibody," as used herein, refers to an immunoglobulin molecule which is able to specifically bind to an epitope. The antibodies in the present invention exist in a variety of forms including, for example, high affinity polyclonal antibodies, monoclonal antibodies, synthetic antibodies, chimeric antibodies, recombinant antibodies and humanized antibodies. Such antibodies originate from immunoglobulin classes IgG, IgM, IgA, IgD and IgE. Such antibodies may be generated using any of a number of methods know in the art. Suitable antibodies may be generated by well-known conventional techniques, e.g. Kohler and Milstein and the many known modifications thereof. Similarly desirable high titer antibodies are generated by applying known recombinant techniques to the monoclonal or polyclonal antibodies developed to these antigens [see, e.g., PCT Patent Application No.

PCT/GB85/00392; British Patent Application Publication No. GB2188638A; Amit *et al.*, 1986 *Science*, 233:747-753; Queen *et al.*, 1989 *Proc. Nat'l. Acad. Sci. USA*, 86:10029-10033; PCT Patent Application No. PCT/WO9007861; and Riechmann *et al.*, *Nature*, 332:323-327 (1988); Huse *et al.*, 1988a *Science*, 246:1275-1281]. Alternatively, antibodies can be produced by manipulating the complementarity determining regions of animal or human antibodies to the antigen of this invention. See, e.g., E. Mark and Padlin, "Humanization of Monoclonal Antibodies", Chapter 4, The Handbook of Experimental Pharmacology, Vol. 113, The Pharmacology of Monoclonal Antibodies, Springer-Verlag (June, 1994); Harlow *et al.*, 1999, Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow *et al.*, 1989, Antibodies: A Laboratory Manual, Cold Spring Harbor, New York;

Houston *et al.*, 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-5883; and Bird *et al.*, 1988, *Science* 242:423-426.

Alternatively, one or more of the C68 capsid proteins of the invention are assembled as multi-antigenic complexes [see, e.g., European Patent Application 0339695, published November 2, 1989] and employed to elicit high titer antibodies. Further provided by the present invention are anti-idiotypic antibodies (Ab2) and anti-anti-idiotypic antibodies (Ab3). See, e.g., M. Wettendorff *et al.*, "Modulation of anti-tumor immunity by anti-idiotypic antibodies." In *Idiotypic Network and Diseases*, ed. by J. Cerny and J. Hiernaux, 1990 *J. Am. Soc. Microbiol.*, Washington DC: pp. 203-229]. These anti-idiotypic and anti-anti-idiotypic antibodies are produced using techniques well known to those of skill in the art. These antibodies may be used for a variety of purposes, including diagnostic and clinical methods and kits.

Under certain circumstances, it may be desirable to introduce a detectable label or a tag onto a C68 antibody or other construct of the invention. As used herein, a detectable label is a molecule which is capable, alone or upon interaction with another molecule, of providing a detectable signal. Most desirably, the label is detectable visually, e.g. by fluorescence, for ready use in immunohistochemical analyses or immunofluorescent microscopy. For example, suitable labels include fluorescein isothiocyanate (FITC), phycoerythrin (PE), allophycocyanin (APC), coriphosphine-O (CPO) or tandem dyes, PE-cyanin-5 (PC5), and PE-Texas Red (ECD). All of these fluorescent dyes are commercially available, and their uses known to the art. Other useful labels include a colloidal gold label. Still other useful labels include radioactive compounds or elements. Additionally, labels include a variety of enzyme systems that operate to reveal a colorimetric signal in an assay, e.g., glucose oxidase (which uses glucose as a substrate) releases peroxide as a product which in the presence of peroxidase and a hydrogen donor such as tetramethyl benzidine (TMB) produces an oxidized TMB that is seen as a blue color. Other examples include horseradish peroxidase (HRP) or alkaline phosphatase (AP), and hexokinase in conjunction with glucose-6-phosphate dehydrogenase which reacts with ATP, glucose, and NAD<sup>+</sup> to yield, among other products, NADH that is detected as increased absorbance at 340 nm wavelength. Other label systems that are utilized in the methods of this invention are detectable by other means, e.g., colored

latex microparticles [Bangs Laboratories, Indiana] in which a dye is embedded are used in place of enzymes to form conjugates with the target sequences provide a visual signal indicative of the presence of the resulting complex in applicable assays.

Methods for coupling or associating the label with a desired molecule are similarly conventional and known to those of skill in the art. Known methods of label attachment are described [see, for example, Handbook of Fluorescent probes and Research Chemicals, 6th Ed., R. P. M. Haugland, Molecular Probes, Inc., Eugene, OR, 1996; Pierce Catalog and Handbook, Life Science and Analytical Research Products, Pierce Chemical Company, Rockford, IL, 1994/1995]. Thus, selection of the label and coupling methods do not limit this invention.

The C68-derived proteins, peptides, and fragments described herein can be produced by any suitable means, including chemical synthesis, or other synthetic means, or by recombinant production and conventional genetic engineering methodologies. For example, peptides can be synthesized by the well known solid phase peptide synthesis methods (Merrifield, *J. Am. Chem. Soc.*, **85**:2149 (1962); Stewart and Young, *Solid Phase Peptide Synthesis* (Freeman, San Francisco, 1969) pp. 27-62). These and other suitable production methods are within the knowledge of those of skill in the art and are not a limitation of the present invention.

Alternatively, suitable methods for recombinant production can be used. Selection of suitable expression systems, including expression vectors and host cells for protein expression and/or viral packaging is within the ability of one of skill in the art and is not a limitation of the present invention. See, e.g., Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press (Cold Spring Harbor, NY).

Nucleic acid sequences for the C68 genome, which is 36521 bp in length, may be obtained using information available in US Patent 6,083,716 and from the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209 (Pan-9). This sequences is also available from GenBank. Other chimpanzee adenovirus sequences are available from the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, and other sources. Desirable chimpanzee strains Pan 5 [ATCC VR-591], Pan 6 [ATCC VR-592], and Pan 7 [ATCC VR-593]. Another particularly

desirable chimpanzee adenovirus strain is chimpanzee adenovirus strain Bertha or C1 [ATCC Accession No. VR-20]. The sequence of the C1 serotype, and the location of the adenovirus genes E1a, E1b, E2a, E2b, E3, E4, L1, L2, L3, L4 and L5 are provided in US Patent 6,083,716, which is incorporated by reference herein. Optionally, non-chimpanzee simian  
5 adenoviral sequences may be used. Such non-chimpanzee adenovirus include those obtained from baboon adenovirus strains [e.g., ATCC VR-275], adenovirus strains isolated from rhesus monkeys [e.g., ATCC VR-209, ATCC VR-275, ATCC VR-353, ATCC VR-355], and adenovirus strains isolated from African green monkeys [e.g., ATCC VR-541; ATCC VR-941; ATCC VR-942; ATCC VR-943]. Alternatively, one may readily select from among the  
10 at least 51 different human serotypes, including, without limitation, human adenovirus serotypes 1, 2, 3, 4, 5, 12, 35, 37, and 40, and other, non-human primate adenovirus serotypes. Further, the sequences of these and other suitable serotypes are available from a variety of databases including, e.g., PubMed and GenBank [see, for example, US Patent No. 5,240,846]. Selection of an appropriate adenovirus is not a limitation of the present  
15 invention.

The invention further provides molecules useful for production of the C68 and C68-derived proteins of the invention, including such molecules which carry polynucleotides including DNA sequences. Thus, the invention further encompasses the nucleic acid sequences encoding the C68-derived constructs of the invention, and molecules and host cells  
20 useful in expression thereof, including suitable DNA molecules and vectors, which can be any suitable genetic element as defined herein. Preferably, these vectors are DNA-based (e.g., plasmids) or viral vectors.

In one embodiment, the C68-derived capsid proteins and other C68 adenovirus proteins described herein are used for non-viral, protein-based delivery of genes, proteins, and  
25 other desirable diagnostic, therapeutic and immunogenic molecules. A desired molecule for delivery to a target cell may be associated with a C68-derived capsid protein or other protein by any suitable means, including, e.g., covalent or non-covalent binding. For example, the C68 penton protein may be readily utilized for such a purpose by production of a fusion protein using the C68 penton sequences of SEQ ID NO:12 in a manner analogous to that  
30 described in Medina-Kauwe LK, et al, *Gene Ther.* 2001 May; 8(10):795-803 and Medina-

Kauwe LK, et al, *Gene Ther.* 2001 Dec; 8(23): 1753-1761. Alternatively, the amino acid sequences of C68 protein IX may be utilized for targeting vectors by associating the protein IX with a ligand that binds to a cell surface receptor, as described in US Patent Appln 20010047081. Suitable ligands include a CD40 antigen, an RGD-containing or polylysine-containing sequence, and the like. Still other C68 proteins may be used for these and similar purposes.

Further, the C68 adenovirus proteins of the invention are particularly well suited for use in producing viral vectors in C68-derived capsids. Suitably, these adenoviruses are pseudotyped such that a nucleic acid molecule carrying adenovirus ITRs from a non-C68 serotype and a minigene are packaged in a C68-derived adenoviral capsid of the invention. Alternatively, adenoviruses may be generated which contain at least the 5' ITRs or the 3' ITRs from C68, in a C68-derived capsid protein. The adenoviral vectors described herein may contain adenoviral sequences derived from one, more than one adenoviral strain. In yet another alternative, other C68 elements described herein may be utilized in production of recombinant vectors, or other desirable constructs.

The C68 proteins of the invention are useful for a variety of purposes, including construction of recombinant viruses. The C68-derived capsid proteins of the invention are useful in producing hybrid vectors, including, hybrid C68-adeno-associated viruses, Epstein-Barr virus, and retroviruses [Caplen *et al*, *Gene Ther.* 6: 454-459 (1999); Tan *et al*, *J Virol.*, 73:7582-7589 (1999)]. Such viruses include C68-derived capsids which encapsidated vectors with adeno-associated virus (AAV) ITRs [Lieber *et al*, *J Virol*, 73:9314-9324 (1999), Recchia *et al*, *Proc Natl Acad Sci USA*, 96:2615-2620 (1999); or lentivirus ITRs (Zheng *et al*, *Nat Biotech*, 18:176-180 (2000), using Maloney leukemia virus long terminal repeats).

In a particularly desirable embodiment, the C68-derived capsid proteins, and optionally, the other C68 sequences described herein, are used to produce recombinant adenoviruses and pseudotyped adenoviruses. However, it will be readily understood that the C68-derived capsid proteins and other novel C68 sequences can be utilized for a variety of purposes, including production of other types of viral vectors (such as, e.g., hybrid vectors) carrying the therapeutic and immunogenic transgenes described below. Additionally, it will be readily understood that viral vectors carrying the unique C68 proteins and other sequences

of the invention can be utilized for targeting and/or delivery of other types of molecules, including proteins, chemical molecules and other moieties useful for diagnostic, therapeutic and/or immunization purposes.

## 5 II. Recombinant Adenoviral Vectors

The compositions of this invention include vectors that deliver a heterologous molecule to cells, either for therapeutic or vaccine purposes. As used herein, a vector may include any genetic element including, without limitation, a cosmid, episome, plasmid, or a virus. In a particularly preferred embodiment, these vectors are viral vectors having capsid  
10 proteins derived from the C68 proteins of the invention. Alternatively, these vectors may contain other C68 sequences of the invention. These viral vectors suitably contain a minigene. By "minigene" is meant the combination of a selected heterologous gene and the other regulatory elements necessary to drive translation, transcription and/or expression of the gene product in a host cell.

15 Typically, an adenoviral vector is designed such that the minigene is flanked on its 5' end and/or its 3' end by adenoviral sequences which include, at a minimum, the cis-elements necessary for replication and virion encapsidation. Thus, in one embodiment, the vector contains adenoviral sequences encompassing at least the 5' end of the adenoviral genome, i.e., the 5' inverted terminal repeat sequences (which functions as origins of replication) and  
20 the native 5' packaging enhancer domains (that contain sequences necessary for packaging linear Ad genomes and enhancer elements for the E1 promoter). The vector is also provided with the cis-acting 3' ITRs. Suitably, the minigene is located between the 5' adenoviral elements and the 3' adenoviral elements. An adenoviral vector of the invention may also contain additional adenoviral sequences. For example, the minigene may be located in the  
25 site of such as the site of a functional E1 deletion or functional E3 deletion, among others that may be selected. Alternatively, the minigene may be inserted into an existing gene region to disrupt the function of that region, if desired.

The term "functionally deleted" or "functional deletion" means that a sufficient amount of the gene region is removed or otherwise damaged, e.g., by mutation or



modification, so that the gene region is no longer capable of producing functional products of gene expression. If desired, the entire gene region may be removed.

Suitably, these adenoviral vectors of the invention contain one or more adenoviral elements derived from C68. In one embodiment, the vectors contain adenoviral ITRs from an adenoviral serotype which differs from C68. Alternatively, C68 ITRs may be utilized in a viral vector of the invention in which the capsid is not naturally occurring, but contains one or more C68 proteins, or fragments thereof. The selection of the serotype of the ITRs and the serotype of any other adenoviral sequences present in vector is not a limitation of the present invention. A variety of adenovirus strains are described herein.

The viral sequences, helper viruses, if needed, and recombinant viral particles, and other vector components and sequences employed in the construction of the vectors described herein are obtained as described above. See, e.g., US Patent No. 5,240,846. The DNA sequences of the adenovirus sequences are employed to construct vectors and cell lines useful in the preparation of such vectors. See, e.g., US Patent No. 6,083,716.

Modifications of the nucleic acid sequences forming the vectors of this invention, including sequence deletions, insertions, and other mutations may be generated using standard molecular biological techniques and are within the scope of this invention.

#### *A. The "Minigene"*

The methods employed for the selection of the transgene, the cloning and construction of the "minigene" and its insertion into the viral vector are within the skill in the art given the teachings provided herein.

##### *1. The transgene*

The transgene is a nucleic acid sequence, heterologous to the vector sequences flanking the transgene, which encodes a polypeptide, protein, or other product, of interest. The nucleic acid coding sequence is operatively linked to regulatory components in a manner which permits transgene transcription, translation, and/or expression in a host cell.

The composition of the transgene sequence will depend upon the use to which the resulting vector will be put. For example, one type of transgene sequence includes a reporter sequence, which upon expression produces a detectable signal. Such reporter sequences include, without limitation, DNA sequences encoding  $\beta$ -lactamase,  $\beta$ -galactosidase

(LacZ), alkaline phosphatase, thymidine kinase, green fluorescent protein (GFP), chloramphenicol acetyltransferase (CAT), luciferase, membrane bound proteins including, for example, CD2, CD4, CD8, the influenza hemagglutinin protein, and others well known in the art, to which high affinity antibodies directed thereto exist or can be produced by

5 conventional means, and fusion proteins comprising a membrane bound protein appropriately fused to an antigen tag domain from, among others, hemagglutinin or Myc. These coding sequences, when associated with regulatory elements which drive their expression, provide signals detectable by conventional means, including enzymatic, radiographic, colorimetric, fluorescence or other spectrographic assays, fluorescent activating cell sorting assays and  
10 immunological assays, including enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and immunohistochemistry. For example, where the marker sequence is the LacZ gene, the presence of the vector carrying the signal is detected by assays for beta-galactosidase activity. Where the transgene is GFP or luciferase, the vector carrying the signal may be measured visually by color or light production in a luminometer.

15 However, desirably, the transgene is a non-marker sequence encoding a product which is useful in biology and medicine, such as proteins, peptides, RNA, enzymes, or catalytic RNAs. Desirable RNA molecules include tRNA, dsRNA, ribosomal RNA, catalytic RNAs, and antisense RNAs. One example of a useful RNA sequence is a sequence which extinguishes expression of a targeted nucleic acid sequence in the treated animal.

20 The transgene may be used for treatment, e.g., of genetic deficiencies, as a cancer therapeutic or vaccine, for induction of an immune response, and/or for prophylactic vaccine purposes. As used herein, induction of an immune response refers to the ability of a molecule (e.g., a gene product) to induce a T cell and/or a humoral immune response to the molecule. The invention further includes using multiple transgenes, e.g., to correct or  
25 ameliorate a condition caused by a multi-subunit protein. In certain situations, a different transgene may be used to encode each subunit of a protein, or to encode different peptides or proteins. This is desirable when the size of the DNA encoding the protein subunit is large, e.g., for an immunoglobulin, the platelet-derived growth factor, or a dystrophin protein. In order for the cell to produce the multi-subunit protein, a cell is infected with the recombinant  
30 virus containing each of the different subunits. Alternatively, different subunits of a protein

may be encoded by the same transgene. In this case, a single transgene includes the DNA encoding each of the subunits, with the DNA for each subunit separated by an internal ribozyme entry site (IRES). This is desirable when the size of the DNA encoding each of the subunits is small, e.g., the total size of the DNA encoding the subunits and the IRES is less than five kilobases. As an alternative to an IRES, the DNA may be separated by sequences encoding a 2A peptide, which self-cleaves in a post-translational event. See, e.g., M.L. Donnelly, *et al*, *J. Gen. Virol.*, 78(Pt 1):13-21 (Jan 1997); Furler, S., *et al*, *Gene Ther.*, 8(11):864-873 (June 2001); Klump H., *et al.*, *Gene Ther.*, 8(10):811-817 (May 2001). This 2A peptide is significantly smaller than an IRES, making it well suited for use when space is a limiting factor. However, the selected transgene may encode any biologically active product or other product, e.g., a product desirable for study.

Suitable transgenes may be readily selected by one of skill in the art. The selection of the transgene is not considered to be a limitation of this invention.

## 2. Regulatory Elements

In addition to the major elements identified above for the minigene, the vector also includes conventional control elements necessary which are operably linked to the transgene in a manner that permits its transcription, translation and/or expression in a cell transfected with the plasmid vector or infected with the virus produced by the invention. As used herein, "operably linked" sequences include both expression control sequences that are contiguous with the gene of interest and expression control sequences that act in *trans* or at a distance to control the gene of interest.

Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation (polyA) signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (i.e., Kozak consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance secretion of the encoded product. A great number of expression control sequences, including promoters which are native, constitutive, inducible and/or tissue-specific, are known in the art and may be utilized.

Examples of constitutive promoters include, without limitation, the retroviral Rous sarcoma virus (RSV) LTR promoter (optionally with the RSV enhancer), the cytomegalovirus (CMV) promoter (optionally with the CMV enhancer) [see, e.g., Boshart *et al*, *Cell*, **41**:521-530 (1985)], the SV40 promoter, the dihydrofolate reductase promoter, the  $\beta$ -actin promoter, the phosphoglycerol kinase (PGK) promoter, and the EF1 $\alpha$  promoter [Invitrogen].

Inducible promoters allow regulation of gene expression and can be regulated by exogenously supplied compounds, environmental factors such as temperature, or the presence of a specific physiological state, e.g., acute phase, a particular differentiation state of the cell, or in replicating cells only. Inducible promoters and inducible systems are available from a variety of commercial sources, including, without limitation, Invitrogen, Clontech and Ariad. Many other systems have been described and can be readily selected by one of skill in the art. For example, inducible promoters include the zinc-inducible sheep metallothionine (MT) promoter and the dexamethasone (Dex)-inducible mouse mammary tumor virus (MMTV) promoter. Other inducible systems include the T7 polymerase promoter system [WO 98/10088]; the ecdysone insect promoter [No *et al*, *Proc. Natl. Acad. Sci. USA*, **93**:3346-3351 (1996)], the tetracycline-repressible system [Gossen *et al*, *Proc. Natl. Acad. Sci. USA*, **89**:5547-5551 (1992)], the tetracycline-inducible system [Gossen *et al*, *Science*, **268**:1766-1769 (1995), see also Harvey *et al*, *Curr. Opin. Chem. Biol.*, **2**:512-518 (1998)]. Other systems include the FK506 dimer, VP16 or p65 using castradiol, diphenol murislerone, the RU486-inducible system [Wang *et al*, *Nat. Biotech.*, **15**:239-243 (1997) and Wang *et al*, *Gene Ther.*, **4**:432-441 (1997)] and the rapamycin-inducible system [Magari *et al*, *J. Clin. Invest.*, **100**:2865-2872 (1997)]. The effectiveness of some inducible promoters increases over time. In such cases one can enhance the effectiveness of such systems by inserting multiple repressors in tandem, e.g., TetR linked to a TetR by an IRES. Alternatively, one can wait at least 3 days before screening for the desired function. Once can enhance expression of desired proteins by known means to enhance the effectiveness of this system. For example, using the Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element (WPRE).

In another embodiment, the native promoter for the transgene will be used. The native promoter may be preferred when it is desired that expression of the transgene should mimic the native expression. The native promoter may be used when expression of the transgene must be regulated temporally or developmentally, or in a tissue-specific manner, or in response to specific transcriptional stimuli. In a further embodiment, other native expression control elements, such as enhancer elements, polyadenylation sites or Kozak consensus sequences may also be used to mimic the native expression.

Another embodiment of the transgene includes a transgene operably linked to a tissue-specific promoter. For instance, if expression in skeletal muscle is desired, a promoter active in muscle should be used. These include the promoters from genes encoding skeletal  $\beta$ -actin, myosin light chain 2A, dystrophin, muscle creatine kinase, as well as synthetic muscle promoters with activities higher than naturally occurring promoters (see Li *et al.*, *Nat. Biotech.*, 17:241-245 (1999)). Examples of promoters that are tissue-specific are known for liver (albumin, Miyatake *et al.*, *J. Virol.*, 71:5124-32 (1997); hepatitis B virus core promoter, Sandig *et al.*, *Gene Ther.*, 3:1002-9 (1996); alpha-fetoprotein (AFP), Arbuthnot *et al.*, *Hum. Gene Ther.*, 7:1503-14 (1996)), bone osteocalcin (Stein *et al.*, *Mol. Biol. Rep.*, 24:185-96 (1997)); bone sialoprotein (Chen *et al.*, *J. Bone Miner. Res.*, 11:654-64 (1996)), lymphocytes (CD2, Hansal *et al.*, *J. Immunol.*, 161:1063-8 (1998); immunoglobulin heavy chain; T cell receptor chain), neuronal such as neuron-specific enolase (NSE) promoter (Andersen *et al.*, *Cell. Mol. Neurobiol.*, 13:503-15 (1993)), neurofilament light-chain gene (Piccioli *et al.*, *Proc. Natl. Acad. Sci. USA*, 88:5611-5 (1991)), and the neuron-specific vgf gene (Piccioli *et al.*, *Neuron*, 15:373-84 (1995)), among others.

Optionally, vectors carrying transgenes encoding therapeutically useful or immunogenic products may also include selectable markers or reporter genes may include sequences encoding geneticin, hygromycin or purimycin resistance, among others. Such selectable reporters or marker genes (preferably located outside the viral genome to be packaged into a viral particle) can be used to signal the presence of the plasmids in bacterial cells, such as ampicillin resistance. Other components of the vector may include an origin of replication. Selection of these and other promoters and vector elements are conventional and many such sequences are available [see, e.g., Sambrook *et al.*, and references cited therein].

These vectors are generated using the techniques and sequences provided herein, in conjunction with techniques known to those of skill in the art.

Such techniques include conventional cloning techniques of cDNA such as those described in texts [Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, NY], use of overlapping oligonucleotide sequences of the adenovirus genomes, polymerase chain reaction, and any suitable method which provides the desired nucleotide sequence.

### III. Production of the Recombinant Viral Particle

In one embodiment, the chimpanzee adenoviral plasmids (or other vectors) are used to produce recombinant adenoviral particles. In one embodiment, the recombinant adenoviruses are functionally deleted in the E1a or E1b genes, and optionally bearing other mutations, e.g., temperature-sensitive mutations or deletions in other genes. In other embodiments, it is desirable to retain an intact E1a and/or E1b region in the recombinant adenoviruses. Such an intact E1 region may be located in its native location in the adenoviral genome or placed in the site of a deletion in the native adenoviral genome (e.g., in the E3 region).

In the construction of useful chimpanzee adenovirus vectors for delivery of a gene to the human (or other mammalian) cell, a range of adenovirus nucleic acid sequences can be employed in the vectors. For example, all or a portion of the adenovirus delayed early gene E3 may be eliminated from the C68 adenovirus sequence which forms a part of the recombinant virus. The function of adenovirus E3 is believed to be irrelevant to the function and production of the recombinant virus particle. Adenovirus vectors may also be constructed having a deletion of at least the ORF6 region of the E4 gene, and more desirably because of the redundancy in the function of this region, the entire E4 region. Still another vector of this invention contains a deletion in the delayed early gene E2a. Deletions may also be made in any of the late genes L1 through L5 of the chimpanzee adenovirus genome. Similarly, deletions in the intermediate genes IX and IVa<sub>2</sub> may be useful for some purposes. Other deletions may be made in the other structural or non-structural adenovirus genes. The above discussed deletions may be used individually, i.e., an adenovirus sequence for use in the present invention may contain deletions in only a single region. Alternatively, deletions

of entire genes or portions thereof effective to destroy their biological activity may be used in any combination. For example, in one exemplary vector, the adenovirus sequence may have deletions of the E1 genes and the E4 gene, or of the E1, E2a and E3 genes, or of the E1 and E3 genes, or of E1, E2a and E4 genes, with or without deletion of E3, and so on. As  
5 discussed above, such deletions may be used in combination with other mutations, such as temperature-sensitive mutations, to achieve a desired result.

An adenoviral vector lacking any essential adenoviral sequences (e.g., E1a, E1b, E2a, E2b, E4 ORF6, L1, L2, L3, L4 and L5) may be cultured in the presence of the missing adenoviral gene products which are required for viral infectivity and propagation of an  
10 adenoviral particle. These helper functions may be provided by culturing the adenoviral vector in the presence of one or more helper constructs (e.g., a plasmid or virus) or a packaging host cell. See, for example, the techniques described for preparation of a "minimal" human Ad vector in International Patent Application WO96/13597, published May 9, 1996, and incorporated herein by reference.

#### 15 1. Helper Viruses

Thus, depending upon the chimpanzee adenovirus gene content of the viral vectors employed to carry the minigene, a helper adenovirus or non-replicating virus fragment may be necessary to provide sufficient chimpanzee adenovirus gene sequences necessary to produce an infective recombinant viral particle containing the minigene. Useful  
20 helper viruses contain selected adenovirus gene sequences not present in the adenovirus vector construct and/or not expressed by the packaging cell line in which the vector is transfected. In one embodiment, the helper virus is replication-defective and contains a variety of adenovirus genes in addition to the sequences described above. Such a helper virus is desirably used in combination with an E1-expressing cell line.

25 Helper viruses may also be formed into poly-cation conjugates as described in Wu *et al*, *J. Biol. Chem.*, 264:16985-16987 (1989); K. J. Fisher and J. M. Wilson, *Biochem. J.*, 299:49 (April 1, 1994). Helper virus may optionally contain a second reporter minigene. A number of such reporter genes are known to the art. The presence of a reporter gene on the helper virus which is different from the transgene on the adenovirus  
30 vector allows both the Ad vector and the helper virus to be independently monitored. This

second reporter is used to enable separation between the resulting recombinant virus and the helper virus upon purification.

## 2. Complementation Cell Lines

To generate recombinant chimpanzee adenoviruses (Ad) deleted in any  
5 of the genes described above, the function of the deleted gene region, if essential to the replication and infectivity of the virus, must be supplied to the recombinant virus by a helper virus or cell line, i.e., a complementation or packaging cell line. In many circumstances, a cell line expressing the human E1 can be used to transcomplement the chimp Ad vector. This is particularly advantageous because, due to the diversity between the chimp Ad sequences of  
10 the invention and the human AdE1 sequences found in currently available packaging cells, the use of the current human E1-containing cells prevents the generation of replication-competent adenoviruses during the replication and production process. However, in certain circumstances, it will be desirable to utilize a cell line which expresses the E1 gene products can be utilized for production of an E1-deleted chimpanzee adenovirus. Such cell lines have  
15 been described. See, e.g., US Patent 6,083,716.

If desired, one may utilize the sequences provided herein to generate a packaging cell or cell line that expresses, at a minimum, the adenovirus E1 gene under the transcriptional control of a promoter for expression in a selected parent cell line. Inducible or constitutive promoters may be employed for this purpose. Examples of such promoters are  
20 described in detail elsewhere in this specification. A parent cell is selected for the generation of a novel cell line expressing any desired Ad gene. Without limitation, such a parent cell line may be HeLa [ATCC Accession No. CCL 2], A549 [ATCC Accession No. CCL 185], KB [CCL 17], Detroit [e.g., Detroit 510, CCL 72] and WI-38 [CCL 75] cells, among others. These cell lines are all available from the American Type Culture Collection, 10801  
25 University Boulevard, Manassas, Virginia 20110-2209. Other suitable parent cell lines may be obtained from other sources.

Such E1-expressing cell lines are useful in the generation of recombinant chimpanzee adenovirus E1 deleted vectors. Additionally, or alternatively, the invention provides cell lines that express one or more chimpanzee adenoviral gene products,  
30 e.g., E1a, E1b, E2a, and/or E4 ORF6, can be constructed using essentially the same



procedures for use in the generation of recombinant chimpanzee viral vectors. Such cell lines can be utilized to transcomplement adenovirus vectors deleted in the essential genes that encode those products, or to provide helper functions necessary for packaging of a helper-dependent virus (e.g., adeno-associated virus). The preparation of a host cell according to this invention involves techniques such as assembly of selected DNA sequences. This assembly may be accomplished utilizing conventional techniques. Such techniques include cDNA and genomic cloning, which are well known and are described in Sambrook et al., cited above, use of overlapping oligonucleotide sequences of the adenovirus genomes, combined with polymerase chain reaction, synthetic methods, and any other suitable methods which provide the desired nucleotide sequence.

In still another alternative, the essential adenoviral gene products are provided in *trans* by the adenoviral vector and/or helper virus. In such an instance, a suitable host cell can be selected from any biological organism, including prokaryotic (e.g., bacterial) cells, and eukaryotic cells, including, insect cells, yeast cells and mammalian cells.

Particularly desirable host cells are selected from among any mammalian species, including, without limitation, cells such as A549, WEHI, 3T3, 10T1/2, 293 cells (which express functional adenoviral E1), Saos, C2C12, L cells, HT1080, HepG2 and primary fibroblast, hepatocyte and myoblast cells derived from mammals including human, monkey, mouse, rat, rabbit, and hamster. The selection of the mammalian species providing the cells is not a limitation of this invention; nor is the type of mammalian cell, i.e., fibroblast, hepatocyte, tumor cell, etc.

### 3. Assembly of Viral Particle and Transfection of a Cell Line

Generally, when delivering the vector comprising the minigene by transfection, the vector is delivered in an amount from about 5  $\mu$ g to about 100  $\mu$ g DNA, and preferably about 10 to about 50  $\mu$ g DNA to about  $1 \times 10^4$  cells to about  $1 \times 10^{13}$  cells, and preferably about  $10^5$  cells. However, the relative amounts of vector DNA to host cells may be adjusted, taking into consideration such factors as the selected vector, the delivery method and the host cells selected.

The vector may be any vector known in the art or disclosed above, including naked DNA, a plasmid, phage, transposon, cosmids, viruses, etc. Introduction into

the host cell of the vector may be achieved by any means known in the art or as disclosed above, including transfection, and infection. One or more of the adenoviral genes may be stably integrated into the genome of the host cell, stably expressed as episomes, or expressed transiently. The gene products may all be expressed transiently, on an episome or stably integrated, or some of the gene products may be expressed stably while others are expressed transiently. Furthermore, the promoters for each of the adenoviral genes may be selected independently from a constitutive promoter, an inducible promoter or a native adenoviral promoter. The promoters may be regulated by a specific physiological state of the organism or cell (i.e., by the differentiation state or in replicating or quiescent cells) or by exogenously-added factors, for example.

Introduction of the molecules (as plasmids or viruses) into the host cell may also be accomplished using techniques known to the skilled artisan and as discussed throughout the specification. In preferred embodiment, standard transfection techniques are used, e.g., CaPO<sub>4</sub> transfection or electroporation.

Assembly of the selected DNA sequences of the adenovirus (as well as the transgene and other vector elements into various intermediate plasmids, and the use of the plasmids and vectors to produce a recombinant viral particle are all achieved using conventional techniques. Such techniques include conventional cloning techniques of cDNA such as those described in texts [Sambrook et al, cited above], use of overlapping oligonucleotide sequences of the adenovirus genomes, polymerase chain reaction, and any suitable method which provides the desired nucleotide sequence. Standard transfection and co-transfection techniques are employed, e.g., CaPO<sub>4</sub> precipitation techniques. Other conventional methods employed include homologous recombination of the viral genomes, plaquing of viruses in agar overlay, methods of measuring signal generation, and the like.

For example, following the construction and assembly of the desired minigene-containing viral vector, the vector is transfected *in vitro* in the presence of a helper virus into the packaging cell line. Homologous recombination occurs between the helper and the vector sequences, which permits the adenovirus-transgene sequences in the vector to be replicated and packaged into virion capsids, resulting in the recombinant viral vector

particles. The current method for producing such virus particles is transfection-based. However, the invention is not limited to such methods.

The resulting recombinant chimpanzee adenoviruses are useful in transferring a selected transgene to a selected cell. In *in vivo* experiments with the recombinant virus grown in the packaging cell lines, the E1-deleted recombinant chimpanzee adenoviral vectors of the invention demonstrate utility in transferring a transgene to a non-chimpanzee, preferably a human, cell.

#### IV. Use of Non-Viral C68 Proteins and C68-derived Adenoviruses

The recombinant adenovirus vectors of the invention are useful for gene transfer to a human or non-chimpanzee veterinary patient *in vitro*, *ex vivo*, and *in vivo*. In addition, a variety of C68 proteins described herein are useful in non-viral targeting of transgenes, proteins, chemical molecules, and other moieties or molecules to cells. Suitable methods of delivery and dosing regimens are readily determined based upon the targeted molecule and targeting protein. Examples of suitable genes and sources of proteins for protein-mediated delivery are provided in the sections below relating to viral delivery of therapeutic and immunogenic molecules. While the discussion below focuses on viral vectors, it will be appreciated that the C68-derived proteins of the invention may be formulated as described herein for the C68-derived viral vectors and the same routes of administration and regimens may be utilized.

The recombinant adenovirus vectors described herein can be used as expression vectors for the production of the products encoded by the heterologous genes *in vitro*. For example, the recombinant adenoviruses containing a gene inserted into the location of an E1 deletion may be transfected into an E1-expressing cell line as described above. Alternatively, replication-competent adenoviruses may be used in another selected cell line. The transfected cells are then cultured in the conventional manner, allowing the recombinant adenovirus to express the gene product from the promoter. The gene product may then be recovered from the culture medium by known conventional methods of protein isolation and recovery from culture.

A C68-derived vector or C68-derived protein of the invention provides an efficient gene transfer vehicle that can deliver a selected transgene or other molecule to a selected host cell *in vivo* or *ex vivo* even where the organism has neutralizing antibodies to one or more AAV serotypes. In one embodiment, the rAAV and the cells are mixed *ex vivo*; the infected cells are cultured using conventional methodologies; and the transduced cells are re-infused into the patient. These compositions are particularly well suited to gene delivery for therapeutic purposes and for immunization, including inducing protective immunity.

More commonly, the C68-derived vectors and C68-derived proteins of the invention will be utilized for delivery of therapeutic or immunogenic molecules, as described below. It will be readily understood for both applications, that the C68-derived constructs of the invention are useful for use in regimens involving single administrations, as well as in regimens involving repeat delivery of adenoviral vectors or non-viral targeted delivery, or repeat delivery of the transgene or other molecule to the cells.

Such regimens typically involve delivery of a series of viral vectors in which the viral capsids are alternated. The viral capsids may be changed for each subsequent administration, or after a pre-selected number of administrations of a particular serotype capsid (e.g., one, two, three, four or more). For example, a regimen may involve delivery of a rAd with a C68-derived capsid and delivery with a rAd with another human or non-human primate adenovirus serotype. Optionally, these regimens may involve administration of rAd with capsids of other non-human primate adenoviruses, human adenoviruses, or artificial serotypes such as are described herein. Alternatively, the regimens involve administration of C68-derived proteins for non-viral targeting with repeat administrations of C68-derived proteins, or with other protein-based delivery systems. Each phase of these regimens can involve administration of a series of injections (or other delivery routes) with a single C68-derived construct followed by a series with another Ad serotype construct. Alternatively, the C68-derived vectors and proteins of the invention may be utilized in regimens involving other non-adenoviral-mediated delivery systems, including other viral systems, non-viral delivery systems, protein, peptides, and other biologically active molecules.

The following sections will focus on exemplary molecules which may be delivered via the adenoviral vectors of the invention.

### A. Ad-Mediated Delivery of Therapeutic Molecules

In one embodiment, the above-described C68-derived constructs are administered to humans according to published methods for gene therapy. A C68-derived construct bearing a transgene can be administered to a patient, preferably suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle. A suitable vehicle includes sterile saline. Other aqueous and non-aqueous isotonic sterile injection solutions and aqueous and non-aqueous sterile suspensions known to be pharmaceutically acceptable carriers and well known to those of skill in the art may be employed for this purpose.

The C68-derived adenoviral vectors are administered in sufficient amounts to transduce the target cells and to provide sufficient levels of gene transfer and expression to provide a therapeutic benefit without undue adverse or with medically acceptable physiological effects, which can be determined by those skilled in the medical arts. Conventional and pharmaceutically acceptable routes of administration include, but are not limited to, direct delivery to the retina and other intraocular delivery methods, direct delivery to the liver, intranasal, intravenous, intramuscular, intratracheal, subcutaneous, intradermal, rectal, oral and other parenteral routes of administration. Routes of administration may be combined, if desired, or adjusted depending upon the transgene or the condition. The route of administration primarily will depend on the nature of the condition being treated.

Dosages of the viral vector will depend primarily on factors such as the condition being treated, the age, weight and health of the patient, and may thus vary among patients. For example, a therapeutically effective adult human or veterinary dosage of the viral vector is generally in the range of from about 100  $\mu$ L to about 100 mL of a carrier containing concentrations of from about  $1 \times 10^6$  to about  $1 \times 10^{15}$  particles, about  $1 \times 10^{11}$  to  $1 \times 10^{13}$  particles, or about  $1 \times 10^9$  to  $1 \times 10^{12}$  particles virus. Dosages will range depending upon the size of the animal and the route of administration. For example, a suitable human or veterinary dosage (for about an 80 kg animal) for intramuscular injection is in the range of about  $1 \times 10^9$  to about  $5 \times 10^{12}$  particles per mL, for a single site. Optionally, multiple sites of administration may be delivered. In another example, a suitable human or veterinary dosage may be in the range of about  $1 \times 10^{11}$  to about  $1 \times 10^{15}$  particles for an oral formulation.

When C68 proteins of the invention are utilized for targeted delivery, suitable dosage ranges, a therapeutically effective adult human or veterinary dosage of the construct is generally in the range of from about 100  $\mu$ L to about 100 mL of a carrier containing concentrations of from about 0.01  $\mu$ g to about 100 mg protein, about 0.1  $\mu$ g to about 10 mg, about 1  $\mu$ g to about 1 mg protein. Dosages will range depending upon the size of the animal and the route of administration. Routes of administration may be readily selected from any suitable route including, without limitation, the routes described above.

One of skill in the art may adjust these doses, depending the route of administration, and the therapeutic or vaccinal application for which the C68-derived construct is employed. The levels of expression of the transgene, or for an immunogen, the level of circulating antibody, can be monitored to determine the frequency of dosage administration. Yet other methods for determining the timing of frequency of administration will be readily apparent to one of skill in the art.

An optional method step involves the co-administration to the patient, either concurrently with, or before or after administration of the C68-derived construct, of a suitable amount of a short acting immune modulator. The selected immune modulator is defined herein as an agent capable of inhibiting the formation of neutralizing antibodies directed against the recombinant vector of this invention or capable of inhibiting cytolytic T lymphocyte (CTL) elimination of the vector. The immune modulator may interfere with the interactions between the T helper subsets ( $T_{H1}$  or  $T_{H2}$ ) and B cells to inhibit neutralizing antibody formation. Alternatively, the immune modulator may inhibit the interaction between  $T_{H1}$  cells and CTLs to reduce the occurrence of CTL elimination of the vector. A variety of useful immune modulators and dosages for use of same are disclosed, for example, in Yang *et al.*, *J. Virol.*, 70(9) (Sept., 1996); International Patent Application No. WO96/12406, published May 2, 1996; and International Patent Application No. PCT/US96/03035, all incorporated herein by reference.

#### 1. Therapeutic Transgenes

Useful therapeutic products encoded by the transgene include hormones and growth and differentiation factors including, without limitation, insulin, glucagon, growth hormone (GH), parathyroid hormone (PTH), growth hormone releasing

factor (GRF), follicle stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (hCG), vascular endothelial growth factor (VEGF), angiopoietins, angiostatin, granulocyte colony stimulating factor (GCSF), erythropoietin (EPO), connective tissue growth factor (CTGF), basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), epidermal growth factor (EGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), insulin growth factors I and II (IGF-I and IGF-II), any one of the transforming growth factor superfamily, including TGF, activins, inhibins, or any of the bone morphogenic proteins (BMP) BMPs 1-15, any one of the heregluin/neuregulin/ARIA/neu differentiation factor (NDF) family of growth factors, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins NT-3 and NT-4/5, ciliary neurotrophic factor (CNTF), glial cell line derived neurotrophic factor (GDNF), neurturin, agrin, any one of the family of semaphorins/collapsins, netrin-1 and netrin-2, hepatocyte growth factor (HGF), ephrins, noggin, sonic hedgehog and tyrosine hydroxylase.

Other useful transgene products include proteins that regulate the immune system including, without limitation, cytokines and lymphokines such as thrombopoietin (TPO), interleukins (IL) IL-1 through IL-18, monocyte chemoattractant protein, leukemia inhibitory factor, granulocyte-macrophage colony stimulating factor, Fas ligand, tumor necrosis factors and, interferons, and, stem cell factor, flk-2/flt3 ligand. Gene products produced by the immune system are also useful in the invention. These include, without limitations, immunoglobulins IgG, IgM, IgA, IgD and IgE, chimeric immunoglobulins, humanized antibodies, single chain antibodies, T cell receptors, chimeric T cell receptors, single chain T cell receptors, class I and class II MHC molecules, as well as engineered immunoglobulins and MHC molecules. Useful gene products also include complement regulatory proteins such as complement regulatory proteins, membrane cofactor protein (MCP), decay accelerating factor (DAF), CR1, CF2 and CD59.

Still other useful gene products include any one of the receptors for the hormones, growth factors, cytokines, lymphokines, regulatory proteins and immune system proteins. The invention encompasses receptors for cholesterol regulation, including the low density lipoprotein (LDL) receptor, high density lipoprotein (HDL) receptor, the very low

density lipoprotein (VLDL) receptor, and the scavenger receptor. The invention also encompasses gene products such as members of the steroid hormone receptor superfamily including glucocorticoid receptors and estrogen receptors, Vitamin D receptors and other nuclear receptors. In addition, useful gene products include transcription factors such as *jun*,  
5 *fos*, max, mad, serum response factor (SRF), AP-1, AP2, *myb*, MyoD and myogenin, ETS-box containing proteins, TFE3, E2F, ATF1, ATF2, ATF3, ATF4, ZF5, NFAT, CREB, HNF-4, C/EBP, SP1, CCAAT-box binding proteins, interferon regulation factor (IRF-1), Wilms tumor protein, ETS-binding protein, STAT, GATA-box binding proteins, e.g., GATA-3, and the forkhead family of winged helix proteins.

10 Other useful gene products include, carbamoyl synthetase I, ornithine transcarbamylase, arginosuccinate synthetase, arginosuccinate lyase, arginase, fumarylacetate hydrolase, phenylalanine hydroxylase, alpha-1 antitrypsin, glucose-6-phosphatase, porphobilinogen deaminase, factor VIII, factor IX, cystathione beta-synthase, branched chain ketoacid decarboxylase, albumin, isovaleryl-coA dehydrogenase, propionyl  
15 CoA carboxylase, methyl malonyl CoA mutase, glutaryl CoA dehydrogenase, insulin, beta-glucosidase, pyruvate carboxylate, hepatic phosphorylase, phosphorylase kinase, glycine decarboxylase, H-protein, T-protein, a cystic fibrosis transmembrane regulator (CFTR) sequence, and a dystrophin cDNA sequence.

Other useful gene products include non-naturally occurring  
20 polypeptides, such as chimeric or hybrid polypeptides having a non-naturally occurring amino acid sequence containing insertions, deletions or amino acid substitutions. For example, single-chain engineered immunoglobulins could be useful in certain immunocompromised patients. Other types of non-naturally occurring gene sequences include antisense molecules and catalytic nucleic acids, such as ribozymes, which could be used to reduce overexpression  
25 of a target.

Reduction and/or modulation of expression of a gene are particularly desirable for treatment of hyperproliferative conditions characterized by hyperproliferating cells, as are cancers and psoriasis. Target polypeptides include those polypeptides which are produced exclusively or at higher levels in hyperproliferative cells as compared to normal  
30 cells. Target antigens include polypeptides encoded by oncogenes such as *myb*, *myc*, *fyn*, and



the translocation gene bcr/abl, ras, src, P53, neu, trk and EGRF. In addition to oncogene products as target antigens, target polypeptides for anti-cancer treatments and protective regimens include variable regions of antibodies made by B cell lymphomas and variable regions of T cell receptors of T cell lymphomas which, in some embodiments, are also used  
5 as target antigens for autoimmune disease. Other tumor-associated polypeptides can be used as target polypeptides such as polypeptides which are found at higher levels in tumor cells including the polypeptide recognized by monoclonal antibody 17-1A and folate binding polypeptides. Such target polypeptides and their ligands are also useful in forming fusion partners with a C68 protein of the invention.

10 Other suitable therapeutic polypeptides and proteins include those which may be useful for treating individuals suffering from autoimmune diseases and disorders by conferring a broad based protective immune response against targets that are associated with autoimmunity including cell receptors and cells which produce self-directed antibodies. T cell mediated autoimmune diseases include Rheumatoid arthritis (RA),  
15 multiple sclerosis (MS), Sjögren's syndrome, sarcoidosis, insulin dependent diabetes mellitus (IDDM), autoimmune thyroiditis, reactive arthritis, ankylosing spondylitis, scleroderma, polymyositis, dermatomyositis, psoriasis, vasculitis, Wegener's granulomatosis, Crohn's disease and ulcerative colitis. Each of these diseases is characterized by T cell receptors (TCRs) that bind to endogenous antigens and initiate the inflammatory cascade associated  
20 with autoimmune diseases.

The C68-derived constructs of the invention are particularly well suited for therapeutic regimens in which multiple deliveries of transgenes is desired, e.g., in regimens involving redelivery of the same transgene or in combination regimens involving delivery of other transgenes. Such regimens may involve administration of a C68-derived  
25 construct, followed by re-administration with a vector from the same serotype adenovirus. Particularly desirable regimens involve administration of a C68-derived construct of the invention, in which the serotype of the viral vector delivered in the first administration differs from the serotype of the viral vector utilized in one or more of the subsequent administrations. For example, a therapeutic regimen involves administration of a C68-  
30 derived vector and repeat administration with one or more adenoviral vectors of the same or

different serotypes. In another example, a therapeutic regimen involves administration of an adenoviral vector followed by repeat administration with a C68-derived vector of the invention which differs from the serotype of the first delivered adenoviral vector, and optionally further administration with another vector which is the same or, preferably, differs from the serotype of the vector in the prior administration steps. These regimens are not limited to delivery of adenoviral vectors constructed using the C68-derived capsids of the invention. Rather, these regimens can readily utilize constructs, including non-viral targeting proteins and viral vectors, from other adenoviral serotypes, including, without limitation, other chimpanzee adenoviral serotypes (e.g., C1, etc), other non-human primate adenoviral serotypes, or human adenoviral serotypes, in combination with one or more of the C68-derived constructs of the invention. Examples of such chimpanzee, other non-human primate and human adenoviral serotypes are discussed elsewhere in this document. Further, these therapeutic regimens may involve either simultaneous or sequential delivery of C68-derived constructs of the invention in combination with non-adenoviral vectors, non-viral vectors, and/or a variety of other therapeutically useful compounds or molecules. The present invention is not limited to these therapeutic regimens, a variety of which will be readily apparent to one of skill in the art.

#### B. Ad-Mediated Delivery of Immunogenic Transgenes

The C68-derived constructs of the invention, including viral vectors and proteins, may also be employed as immunogenic compositions. As used herein, an immunogenic composition is a composition to which a humoral (e.g., antibody) or cellular (e.g., a cytotoxic T cell) response is mounted to a transgene product delivered by the immunogenic composition following delivery to a mammal, and preferably a primate. The present invention provides a recombinant C68-derived Ad that can contain in any of its adenovirus sequence deletions a gene encoding a desired immunogen, or a C68 protein capable of targeting an immunogenic molecule. The C68-derived adenovirus is well suited for use as a live recombinant virus vaccine in different animal species compared to an adenovirus of human origin, but is not limited to such a use. The recombinant adenoviruses and C68 proteins can be used as prophylactic or therapeutic vaccines against any pathogen for

which the antigen(s) crucial for induction of an immune response and able to limit the spread of the pathogen has been identified and for which the cDNA is available.

Such vaccinal (or other immunogenic) compositions are formulated in a suitable delivery vehicle, as described above. Generally, doses for the immunogenic compositions are in the range defined above for therapeutic compositions. The levels of immunity of the selected gene can be monitored to determine the need, if any, for boosters. Following an assessment of antibody titers in the serum, optional booster immunizations may be desired.

Optionally, a vaccinal composition of the invention may be formulated to contain other components, including, e.g. adjuvants, stabilizers, pH adjusters, preservatives and the like. Such components are well known to those of skill in the vaccine art. Examples of suitable adjuvants include, without limitation, liposomes, alum, monophosphoryl lipid A, and any biologically active factor, such as cytokine, an interleukin, a chemokine, a ligands, and optimally combinations thereof. Certain of these biologically active factors can be expressed *in vivo*, e.g., via a polynucleotide, plasmid or viral vector. For example, such an adjuvant can be administered with a priming DNA vaccine encoding an antigen to enhance the antigen-specific immune response compared with the immune response generated upon priming with a DNA vaccine encoding the antigen only.

The recombinant adenoviruses are administered in a "an immunogenic amount", that is, an amount of recombinant adenovirus that is effective in a route of administration to transfect the desired cells and provide sufficient levels of expression of the selected gene to induce an immune response. Where protective immunity is provided, the recombinant adenoviruses are considered to be vaccine compositions useful in preventing infection and/or recurrent disease.

Alternatively, or in addition, the vectors of the invention may contain, or C68-capsid or other protein can be utilized to target a transgene encoding a peptide, polypeptide or protein which induces an immune response to a selected immunogen. The C68-derived viruses of this invention are expected to be highly efficacious at inducing cytolytic T cells and antibodies to the inserted heterologous antigenic protein expressed by the vector.

# 1. Immunogenic Transgenes

For example, immunogens may be selected from a variety of viral families. Example of desirable viral families against which an immune response would be desirable include, the picornavirus family, which includes the genera rhinoviruses, which are responsible for about 50% of cases of the common cold; the genera enteroviruses, which include polioviruses, coxsackieviruses, echoviruses, and human enteroviruses such as hepatitis A virus; and the genera aphthoviruses, which are responsible for foot and mouth diseases, primarily in non-human animals. Within the picornavirus family of viruses, target antigens include the VP1, VP2, VP3, VP4, and VPG. Another viral family includes the calcivirus family, which encompasses the Norwalk group of viruses, which are an important causative agent of epidemic gastroenteritis. Still another viral family desirable for use in targeting antigens for inducing immune responses in humans and non-human animals is the togavirus family, which includes the genera alphavirus, which include Sindbis viruses, Ross River virus, and Venezuelan, Eastern & Western Equine encephalitis, and rubivirus, including Rubella virus. The flaviviridae family includes dengue, yellow fever, Japanese encephalitis, St. Louis encephalitis and tick borne encephalitis viruses. Other target antigens may be generated from the Hepatitis C or the coronavirus family, which includes a number of non-human viruses such as infectious bronchitis virus (poultry), porcine transmissible gastroenteric virus (pig), porcine hemagglutinating encephalomyelitis virus (pig), feline infectious peritonitis virus (cats), feline enteric coronavirus (cat), canine coronavirus (dog), and human respiratory coronaviruses, which may cause the common cold and/or non-A, B or C hepatitis. Within the coronavirus family, target antigens include the E1 (also called M or matrix protein), E2 (also called S or Spike protein), E3 (also called HE or hemagglutinin-esterase) glycoprotein (not present in all coronaviruses), or N (nucleocapsid). Still other antigens may be targeted against the rhabdovirus family, which includes the genera vesiculovirus (e.g., Vesicular Stomatitis Virus), and the general lyssavirus (e.g., rabies). Within the rhabdovirus family, suitable antigens may be derived from the G protein or the N protein. The family filoviridae, which includes hemorrhagic fever viruses such as Marburg and Ebola virus may be a suitable source of antigens. The paramyxovirus family includes parainfluenza Virus Type 1, parainfluenza Virus Type 3, bovine parainfluenza Virus Type 3,

rubulavirus (mumps virus), parainfluenza Virus Type 2, parainfluenza virus Type 4, Newcastle disease virus (chickens), rinderpest, morbillivirus, which includes measles and canine distemper, and pneumovirus, which includes respiratory syncytial virus. The influenza virus is classified within the family orthomyxovirus and is a suitable source of antigen (e.g., the HA protein, the N1 protein). The bunyavirus family includes the genera bunyavirus (California encephalitis, La Crosse), phlebovirus (Rift Valley Fever), hantavirus (puremala is a hemahagin fever virus), nairovirus (Nairobi sheep disease) and various unassigned bungaviruses. The arenavirus family provides a source of antigens against LCM and Lassa fever virus. The reovirus family includes the genera reovirus, rotavirus (which causes acute gastroenteritis in children), orbiviruses, and cultivirus (Colorado Tick fever, Lebombo (humans), equine encephalosis, blue tongue).

The retrovirus family includes the sub-family oncorivirinal which encompasses such human and veterinary diseases as feline leukemia virus, HTLVI and HTLVII, lentivirinal (which includes human immunodeficiency virus (HIV), simian immunodeficiency virus (SIV), feline immunodeficiency virus (FIV), equine infectious anemia virus, and spumavirinal). Among the lentiviruses, many suitable antigens have been described and can readily be selected. Examples of suitable HIV and SIV antigens include, without limitation the gag, pol, Vif, Vpx, VPR, Env, Tat, Nef, and Rev proteins, as well as various fragments thereof. For example, suitable fragments of the Env protein may include any of its subunits such as the gp120, gp160, gp41, or smaller fragments thereof, e.g., of at least about 8 amino acids in length. Similarly, fragments of the tat protein may be selected. [See, US Patent 5,891,994 and US Patent 6,193,981.] See, also, the HIV and SIV proteins described in D.H. Barouch et al, J. Virol., 75(5):2462-2467 (March 2001), and R.R. Amara, et al, *Science*, 292:69-74 (6 April 2001). In another example, the HIV and/or SIV immunogenic proteins or peptides may be used to form fusion proteins or other immunogenic molecules. See, e.g., the HIV-1 Tat and/or Nef fusion proteins and immunization regimens described in WO 01/54719, published August 2, 2001, and WO 99/16884, published April 8, 1999. The invention is not limited to the HIV and/or SIV immunogenic proteins or peptides described herein. In addition, a variety of modifications to these proteins have been described or could readily be made by one of skill in the art. See, e.g., the modified gag protein that is described

in US Patent 5,972,596. Further, any desired HIV and/or SIV immunogens may be delivered alone or in combination. Such combinations may include expression from a single vector or from multiple vectors. Optionally, another combination may involve delivery of one or more expressed immunogens with delivery of one or more of the immunogens in protein form.

5 Such combinations are discussed in more detail below.

The papovavirus family includes the sub-family polyomaviruses (BKU and JCU viruses) and the sub-family papillomavirus (associated with cancers or malignant progression of papilloma). The adenovirus family includes viruses (EX, AD7, ARD, O.B.) which cause respiratory disease and/or enteritis. The parvovirus family feline parvovirus (feline enteritis), feline panleucopeniavirus, canine parvovirus, and porcine parvovirus. The herpesvirus family includes the sub-family alphaherpesvirinae, which encompasses the genera simplexvirus (HSVI, HSVII), varicellovirus (pseudorabies, varicella zoster) and the sub-family betaherpesvirinae, which includes the genera cytomegalovirus (HCMV, muromegalovirus) and the sub-family gammaherpesvirinae, which includes the genera lymphocryptovirus, EBV (Burkitts lymphoma), infectious rhinotracheitis, Marek's disease virus, and rhadinovirus. The poxvirus family includes the sub-family chordopoxvirinae, which encompasses the genera orthopoxvirus (Variola (Smallpox) and Vaccinia (Cowpox)), parapoxvirus, avipoxvirus, capripoxvirus, leporipoxvirus, suipoxvirus, and the sub-family entomopoxvirinae. The hepadnavirus family includes the Hepatitis B virus. One unclassified virus which may be suitable source of antigens is the Hepatitis delta virus. Still other viral sources may include avian infectious bursal disease virus and porcine respiratory and reproductive syndrome virus. The alphavirus family includes equine arteritis virus and various Encephalitis viruses.

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The present invention may also encompass immunogens which are useful to immunize a human or non-human animal against other pathogens including bacteria, fungi, parasitic microorganisms or multicellular parasites which infect human and non-human vertebrates, or from a cancer cell or tumor cell. Examples of bacterial pathogens include pathogenic gram-positive cocci include pneumococci; staphylococci; and streptococci. Pathogenic gram-negative cocci include meningococcus; gonococcus. Pathogenic enteric gram-negative bacilli include enterobacteriaceae; pseudomonas, acinetobacteria and

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eikenella; melioidosis; salmonella; shigella; haemophilus; moraxella; *H. ducreyi* (which causes chancroid); brucella; *Francisella tularensis* (which causes tularemia); yersinia (pasteurella); streptobacillus moniliformis and spirillum; Gram-positive bacilli include listeria monocytogenes; erysipelotheix rhusiopathiae; *Corynebacterium diphtheria* (diphtheria);  
 5 cholera; *B. anthracis* (anthrax); donovanosis (granuloma inguinale); and bartonellosis.

Diseases caused by pathogenic anaerobic bacteria include tetanus; botulism; other clostridia; tuberculosis; leprosy; and other mycobacteria. Pathogenic spirochetal diseases include syphilis; treponematoses: yaws, pinta and endemic syphilis; and leptospirosis. Other infections caused by higher pathogen bacteria and pathogenic fungi include actinomycosis;

10 nocardiosis; cryptococcosis, blastomycosis, histoplasmosis and coccidioidomycosis; candidiasis, aspergillosis, and mucormycosis; sporotrichosis; paracoccidioidomycosis, petriellidiosis, torulopsosis, mycetoma and chromomycosis; and dermatophytosis. Rickettsial infections include Typhus fever, Rocky Mountain spotted fever, Q fever, and Rickettsialpox.

Examples of mycoplasma and chlamydial infections include: mycoplasma pneumoniae;

15 lymphogranuloma venereum; psittacosis; and perinatal chlamydial infections. Pathogenic eukaryotes encompass pathogenic protozoans and helminths and infections produced thereby include: amebiasis; malaria; leishmaniasis; trypanosomiasis; toxoplasmosis; *Pneumocystis carinii*; *Trichans*; *Toxoplasma gondii*; babesiosis; giardiasis; trichinosis; filariasis; schistosomiasis; nematodes; trematodes or flukes; and cestode (tapeworm) infections.

20 Many of these organisms and/or toxins produced thereby have been identified by the Centers for Disease Control [(CDC), Department of Health and Human Services, USA], as agents which have potential for use in biological attacks. For example, some of these biological agents, include, *Bacillus anthracis* (anthrax), *Clostridium botulinum* and its toxin (botulism), *Yersinia pestis* (plague), variola major (smallpox), *Francisella tularensis* (tularemia), and viral hemorrhagic fever, all of which are currently classified as  
 25 Category A agents; *Coxiella burnetti* (Q fever); Brucella species (brucellosis), *Burkholderia mallei* (glanders), *Ricinus communis* and its toxin (ricin toxin), *Clostridium perfringens* and its toxin (epsilon toxin), *Staphylococcus* species and their toxins (enterotoxin B), all of which are currently classified as Category B agents; and Nippan virus, multidrug-resistant  
 30 tuberculosis, yellow fever, tickborne hemorrhagic fever viruses, tickborne encephalitis

viruses, and hantaviruses, which are currently classified as Category C agents. In addition, other organisms, which are so classified or differently classified, may be identified and/or used for such a purpose in the future. It will be readily understood that the viral vectors and other constructs described herein are useful to deliver antigens from these organisms, viruses, their toxins or other by-products, which will prevent and/or treat infection or other adverse reactions with these biological agents.

Administration of the vectors and proteins of the invention to deliver immunogens against the variable region of the T cells elicit an immune response including CTLs to eliminate those T cells. In RA, several specific variable regions of TCRs which are involved in the disease have been characterized. These TCRs include V-3, V-14, V-17 and V $\alpha$ -17. Thus, delivery of a nucleic acid sequence that encodes at least one of these polypeptides will elicit an immune response that will target T cells involved in RA. In MS, several specific variable regions of TCRs which are involved in the disease have been characterized. These TCRs include V-7 and V $\alpha$ -10. Thus, delivery of a nucleic acid sequence that encodes at least one of these polypeptides will elicit an immune response that will target T cells involved in MS. In scleroderma, several specific variable regions of TCRs which are involved in the disease have been characterized. These TCRs include V-6, V-8, V-14 and V $\alpha$ -16, V $\alpha$ -3C, V $\alpha$ -7, V $\alpha$ -14, V $\alpha$ -15, V $\alpha$ -16, V $\alpha$ -28 and V $\alpha$ -12. Thus, delivery of a recombinant chimpanzee adenovirus that encodes at least one of these polypeptides will elicit an immune response that will target T cells involved in scleroderma.

### C. Ad-Mediated Delivery Methods

The therapeutic levels, or levels of immunity, of the selected gene can be monitored to determine the need, if any, for boosters. Following an assessment of CD8+ T cell response, or optionally, antibody titers, in the serum, optional booster immunizations may be desired. Optionally, the C68-derived constructs of the invention may be delivered in a single administration or in various combination regimens, e.g., in combination with a regimen or course of treatment involving other active ingredients or in a prime-boost regimen. A variety of such regimens have been described in the art and may be readily selected.

For example, prime-boost regimens may involve the administration of a DNA (e.g., plasmid) based vector to prime the immune system to second, booster, administration



with a traditional antigen, such as a protein or a recombinant virus carrying the sequences encoding such an antigen. See, e.g., WO 00/11140, published March 2, 2000, incorporated by reference. Alternatively, an immunization regimen may involve the administration of a recombinant chimpanzee adenoviral vector of the invention to boost the immune response to  
5 a vector (either viral or DNA-based) carrying an antigen, or a protein. In still another alternative, an immunization regimen involves administration of a protein followed by booster with a vector encoding the antigen.

In one embodiment, the invention provides a method of priming and boosting an immune response to a selected antigen by delivering a plasmid DNA vector carrying said  
10 antigen, followed by boosting with a recombinant chimpanzee adenoviral vector of the invention. In one embodiment, the prime-boost regimen involves the expression of multiproteins from the prime and/or the boost vehicle. See, e.g., R.R. Amara, *Science*, **292**:69-74 (6 April 2001) which describes a multiprotein regimen for expression of protein subunits useful for generating an immune response against HIV and SIV. For example, a  
15 DNA prime may deliver the Gag, Pol, Vif, VPX and Vpr and Env, Tat, and Rev from a single transcript. Alternatively, the SIV Gag, Pol and HIV-1 Env is delivered in a recombinant adenovirus construct of the invention. Still other regimens are described in WO 99/16884 and WO 01/54719.

However, the prime-boost regimens are not limited to immunization for HIV  
20 or to delivery of these antigens. For example, priming may involve delivering with a first chimp vector of the invention followed by boosting with a second chimp vector, or with a composition containing the antigen itself in protein form. In one example, the prime-boost regimen can provide a protective immune response to the virus, bacteria or other organism from which the antigen is derived. In another desired embodiment, the prime-boost regimen  
25 provides a therapeutic effect that can be measured using convention assays for detection of the presence of the condition for which therapy is being administered.

The priming composition may be administered at various sites in the body in a dose dependent manner, which depends on the antigen to which the desired immune response is being targeted. The invention is not limited to the amount or situs of injection(s) or to the  
30 pharmaceutical carrier. Rather, the regimen may involve a priming and/or boosting step,

each of which may include a single dose or dosage that is administered hourly, daily, weekly or monthly, or yearly. As an example, the mammals may receive one or two doses containing between about 10  $\mu\text{g}$  to about 50  $\mu\text{g}$  of plasmid in carrier. A desirable amount of a DNA composition ranges between about 1  $\mu\text{g}$  to about 10,000  $\mu\text{g}$  of the DNA vector. Dosages may vary from about 1  $\mu\text{g}$  to 1000  $\mu\text{g}$  DNA per kg of subject body weight. The amount or site of delivery is desirably selected based upon the identity and condition of the mammal.

The dosage unit of the vector suitable for delivery of the antigen to the mammal is described herein. The vector is prepared for administration by being suspended or dissolved in a pharmaceutically or physiologically acceptable carrier such as isotonic saline; isotonic salts solution or other formulations that will be apparent to those skilled in such administration. The appropriate carrier will be evident to those skilled in the art and will depend in large part upon the route of administration. The compositions of the invention may be administered to a mammal according to the routes described above, in a sustained release formulation using a biodegradable biocompatible polymer, or by on-site delivery using micelles, gels and liposomes. Optionally, the priming step of this invention also includes administering with the priming composition, a suitable amount of an adjuvant, such as are defined herein.

Preferably, a boosting composition is administered about 2 to about 27 weeks after administering the priming composition to the mammalian subject. The administration of the boosting composition is accomplished using an effective amount of a boosting composition containing or capable of delivering the same antigen as administered by the priming DNA vaccine. The boosting composition may be composed of a recombinant viral vector derived from the same viral source (e.g., adenoviral sequences of the invention) or from another source. Alternatively, the "boosting composition" can be a composition containing the same antigen as encoded in the priming DNA vaccine, but in the form of a protein or peptide, which composition induces an immune response in the host. In another embodiment, the boosting composition contains a DNA sequence encoding the antigen under the control of a regulatory sequence directing its expression in a mammalian cell, e.g., vectors such as well-known bacterial or viral vectors. The primary requirements of the boosting

composition are that the antigen of the composition is the same antigen, or a cross-reactive antigen, as that encoded by the priming composition.

In another embodiment, the chimpanzee adenoviral vectors and C68 targeting proteins of the invention are also well suited for use in a variety of other immunization and therapeutic regimens. Such regimens may involve delivery of C68 constructs of the invention simultaneously or sequentially with Ad constructs of different serotype capsids, regimens in which C68-derived constructs of the invention are delivered simultaneously or sequentially with non-Ad vectors, regimens in which the adenoviral vectors of the invention are delivered simultaneously or sequentially with proteins, peptides, and/or other biologically useful therapeutic or immunogenic compounds. Such uses will be readily apparent to one of skill in the art.

#### V. Method for Rapid Screening of Bacterial Transformants

An elegant selection method is provided by the present invention, which permits the rapid screening of constructs produced by homologous recombination or direct cloning methods. As used herein, these constructs are preferably viruses, but may include other types of vectors, such as a cosmid, episome, plasmid, or other genetic element that delivers a heterologous molecule to cells.

In one desired embodiment, the method utilizes the gene encoding green fluorescent protein (GFP), to provide a green-white selection method in which the presence of a recombinant is detected by the absence of GFP expression (i.e., the recombinants are observed as white in a green background). Alternatively, the method may utilize another suitable marker genes, including, without limitation, other fluorescent proteins and luciferase.

In one example, the method is used for production of a recombinant construct from homologous recombination of co-transected vectors into a selected host cell. As used herein, a host cell may be readily selected from an biological organism, including prokaryotic and eukaryotic cells, such as those discussed in the section related to production of a recombinant viral particle. Selection of the host cell is not a limitation of the present invention.

Suitably, each of the vectors contains the marker gene (e.g., GFP) under the control of a promoter that directs expression thereof in a host cell. Alternatively, each of the parental

vectors may contain a different marker gene that allows them to be distinguished not only from the recombinant construct produced, but also from each other. Preferably, where prokaryotic GFP is utilized, it is under the control of a prokaryotic promoter such as the promoter from lacZ. However, other suitable prokaryotic or non-prokaryotic promoters may be readily selected from among the promoters described herein and known to those of skill in the art. Advantageously, the GFP protein is placed in the portion of the vectors that are eliminated during homologous recombination and thus, the GFP protein is absent from the recombinant vector produced. In this manner, the presence of unrecombined parental vectors are readily detected under a phase contrast fluorescent microscope (or other suitable detection means) as expressing the marker gene and the recombinant constructs lack expression of the marker. In the methods in which both parent vectors utilize GFP, the recombinant appears as white in a background of green.

In another example, the method is used for production of a recombinant construct involving homologous recombination, in which the host cell stably contains at least one of the parental constructs to be utilized for production of the recombinant construct. In this embodiment, the host cell can be subjected to a single transfection. In still other embodiments, the method of the invention may be utilized for triple transfections. As with the double transfection described above, the parental constructs may contain the same marker gene or may contain different marker genes.

In another example, the method of the invention is used from production of a recombinant construct by direct cloning. Suitably, in this embodiment, the marker gene is present in that portion of the parent construct which is deleted during the cloning process. For example, the marker gene expression cassette (i.e., the gene, promoter, and any other necessary regulatory sequences) is engineered into the E1- or E3-region of an adenoviral vector, into which a transgene or minigene cassette will be cloned. The success of direct cloning into the target region can be readily detected by the absence of marker gene expression.

Optionally, the method of the invention can be readily assembled in the form of a kit which is available in a commercially useful format for production of recombinant constructs, e.g., recombinant adenoviruses. Typically, such kits will include plasmid backbones

containing a desired viral genome containing a marker gene inserted at a point upstream or downstream of the recombination site, as appropriate, or a plasmid backbone containing the marker gene inserted at the splice site for direct cloning of a heterologous gene. Such a kit can further include appropriate culture media, host cells, a test control, instructions, and other suitable materials.

In the examples below, this method is used in production of adenoviruses. However, it will be readily understood that this method may be readily adapted for use in generating other types of adenoviral, or non-adenoviral viral vectors.

The following examples are provided to illustrate the invention and do not limit the scope thereof. One skilled in the art will appreciate that although specific reagents and conditions are outlined in the following examples, modifications can be made which are meant to be encompassed by the spirit and scope of the invention.

#### **Example 1 - Creation of an E1 deleted vector based on Chimpanzee Adenovirus C68 Using Green-white Selection Of Recombinants**

A replication defective version of C68 was isolated for use in gene transfer. The classic strategy of creating a recombinant with E1 deleted, by homologous recombination in an E1 expressing cell line was pursued. The first step was creation of a plasmid containing m.u. 0 through 1.3 followed by addition of a minigene expressing enhanced green fluorescent protein (GFP) from a CMV promoter and C68 sequence spanning 9-16.7 m.u. This linearized plasmid was cotransfected into an E1 expressing cell line with Ssp I-digested C68 plasmid (SspI cuts at 3.6 m.u. leaving 4644 bp for homologous recombination). Experiments were initially conducted with 293 cells which harbor E1 from human Ad5 with the hope that this would suffice for transcomplementation. Indeed, plaques formed which represented the desired recombinant. The resulting vector was called C68-CMV-GFP.

The strategy for generating recombinants was modified to enable efficient and rapid isolation of recombinants. First, the alkaline phosphatase DNA in the initial shuttle vector was replaced with a prokaryotic GFP gene driven by the prokaryotic promoter from lacZ.

This allowed efficient screening of bacterial transformations when attempting to incorporate a desired eukaryotic RNA pol II transcriptional unit into the shuttle vector. The resulting transformation can be screened for expression of GFP; white colonies are recombinants while green colonies are residual parental plasmid.

5 A green-white selection has been used to screen the products of cotransfection for the isolation of human Ad5 recombinants (A.R. Davis et al, *Gene Thera.*, 5:1148-1152 (1998)). In the present system, and in contrast to Davis, the initial shuttle vector was revised to include extended 3' sequences from 9 to 26 MU. This vector was cotransfected with viral DNA from the original C68-CMV-GFP isolate that had been restricted with Xba I, which cuts at MU  
10 16.5 allowing for 9.5 Kb of overlap for homologous recombination. The resulting plaques were screened under a phase contrast fluorescent microscope for non-fluorescing isolates that represent the desired recombinants. This greatly simplified screening in comparison to the standard methods based on structure or transgene expression. Thus, this method may be readily adapted for use in generating other types of adenoviral, or non-adenoviral viral  
15 vectors.

#### A. Shuttle Plasmid

To construct a plasmid shuttle vector for creation of recombinant C68 virus, the plasmid pSP72 (Promega, Madison, WI) was modified by digestion with Bgl II followed by filling-in of the ends with Klenow enzyme (Boehringer Mannheim, Indianapolis, IN) and  
20 ligation with a synthetic 12 bp Pac I linker (New England Biolabs, Beverly, MA) to yield pSP72-Pac. A 456 bp Pac I/SnaB I fragment spanning map unit (m.u. or MU) 0-1.3 of the C68 genome was isolated from the pNEB-BamE plasmid containing BamHI E fragment of the C68 genome and cloned into Pac I and EcoR V treated pSP72-Pac to yield pSP-C68-MU 0-1.3. A minigene cassette consisting of the cytomegalovirus early promoter driving lacZ with  
25 a SV40 poly A signal was separated from pCMV $\beta$  (Clontech, Palo Alto, CA) as a 4.5 kb EcoRI/SalI fragment and ligated to pSP-C68-MU 0-1.3 restricted with the same set of enzymes, resulting in pSP-C68-MU 0-1.3-CMVlacZ.

For the initial step in the isolation of the 9-16.7 MU region of C68, both pGEM-3Z (Promega, Madison, MI) and pBS-C68-BamF were double-digested with BamHI  
30 and Sph I enzymes. Then the 293 bp fragment from pBS-C68-BamF was ligated with pGEM-

3Z backbone to form pGEM-C68-MU 9-9.8. A 2.4 kb fragment including the C68 MU 9.8-16.7 was obtained from the pBS-C68 BamHB clone after XbaI digestion, filling in reaction and subsequent BamHI treatment and cloned into BamHI/SmaI double digested pGEM-C68-MU 9-9.8 to generate pGEM-C68-MU 9-16.7. The C68 9-16.7 m.u. region was isolated from pGEM-C68-MU 9-16.7 by digestion with EcoRI, filling in of the ends with Klenow enzyme (Boehringer Mannheim, Indianapolis, IN), ligation of a synthetic 12 bp HindIII linker (NEB) and then digestion with HindIII. This 2.7 kb fragment spanning the C68 MU 9-16.7 was cloned into the HindIII site of pSP-C68-MU 0-1.3-CMVlacZ to form the final shuttle plasmid pC68-CMV-LacZ. In addition, an 820 bp alkaline phosphatase (AP) cDNA fragment was isolated from pAdCMVALP (K. J. Fisher, et al., *J. Virol.*, 70:520-532 (1996)) and exchanged for lacZ at Not I sites of pC68-CMV-lacZ, resulting in pC68-CMV-AP.

#### B. Construction of Recombinant Virus

To create the E1-deleted recombinant C68-CMVEGFP vector, a pC68-CMV-EGFP shuttle plasmid was first constructed by replacing the lacZ transgene in pC68-CMV-lacZ with the enhanced green fluorescent protein (EGFP) gene. The replacement cloning process was carried out as the follows. An additional NotI restriction site was introduced into the 5' end of the EGFP coding sequence in the pEGFP-1 (Clontech, Palo Alto, CA) by BamHI digestion, filling in reaction and ligation of a 8 bp synthetic NotI linker (NEB). After NotI restriction of both constructs, the EGFP sequence was isolated from the modified pEGFP-1 and used to replace the lacZ gene in the pC68-CMV-lacZ. The pC68-CMVEGFP construct (3 µg) was co-transfected with Ssp I-digested C68 genomic DNA (1 µg) into 293 cells for homologous recombination as previously described (G. Gao, et al., *J. Virol.*, 70:8934-8943 (1996)). Green plaques visualized by fluorescent microscopy were isolated for 2 rounds of plaque purification, expansion and purification by CsCl gradient sedimentation (G. Gao, et al., cited above).

The invention provides a uniquely modified version of the green/white selection process (A. R. Davis, et al., *Gene Thera.*, 5:1148-1152 (1998)). The present example illustrates use of this method for construction of recombinant C68 vectors. A 7.2 kb fragment spanning 9 to 36 MU was isolated from the pBSC68-BamB plasmid by treatment with AgeI and BsiwI restriction endonucleases and cloned into Asp718 and AgeI sites of

pC68-CMV-AP shuttle plasmid, resulting in a new plasmid called pC68CMV-AP-MU36. A further modification was made to remove 26 to 36 m.u. from pC68CMV-AP-MU36 by Eco47III and NruI digestions. The new shuttle plasmid called pC68CMV-AP-MU26 has a shorter region for homologous recombination (i.e., 16.7-26 MU) 3' to the minigene. To make a recombinant C68 vector, alkaline phosphatase (AP) is replaced with the gene of interest. The resulting pC68CMV-Nugene-MU26 construct is co-transfected with Xba I (16.5 MU) restricted C68-CMVGFP viral DNA into 293 cells, followed by top agar overlay. The recombinant virus plaques (white) are generated through the homologous recombination in the region of 16.7-26 MU which is shared between pC68CMV-Nugene construct and C68 viral backbone; the recombinants which form white plaques are selected from green plaques of uncut C68-CMVGFP virus.

The green/white selection mechanism was also introduced to the process of cloning of the gene of interest into the pC68 shuttle plasmid. The AP gene in both pC68CMV-AP-MU36 and pC68CMV-AP-MU26 was replaced with a cassette of prokaryotic GFP gene driven by the lacZ promoter isolated from pGFP-MU31 (Clontech, Palo Alto, CA). Thus, white colonies of bacterial transformants will contain the recombinant plasmid. This green/white selection process for bacterial colonies circumvented the need for making and characterizing large numbers of miniprep DNAs and so further enhanced the efficiency in creating recombinant C68 vectors.

## Example 2 - Chimpanzee C68 Virus Stock and Replication

Examples 3 through 5 which follow provide additional characterization of the chimpanzee C68. It will be appreciated by one of skill in the art that this information can be readily used in the construction of novel recombinant chimpanzee adenoviral constructs.

The C68 virus stock was obtained from ATCC (Rockville, MD) and propagated in 293 cells (ATCC) cultured in DMEM (Sigma, St. Louis, MO) supplemented with 10% fetal calf serum (FCS; Sigma or Hyclone, Logan, UT) and 1% Penicillin-Streptomycin (Sigma). Infection of 293 cells was carried out in DMEM supplemented with 2% FCS for the first 24 hours, after which FCS was added to bring the final concentration to 10%. Infected cells were harvested when 100% of the cells exhibited virus-induced cytopathic effect (CPE),



collected, and concentrated by centrifugation. Cell pellets were resuspended in 10mM Tris (pH 8.0), and lysed by 3 cycles of freezing and thawing. Virus preparations were obtained following 2 ultra centrifuge steps on cesium chloride density gradients and stocks of virus were diluted to  $1 \times 10^{12}$  particles/ml in 10mM Tris/100mM NaCl/50% glycerol and stored at  
 5 -70 °C.

### Example 3 - Cloning and sequencing of viral genomic DNA

Genomic DNA was isolated from the purified virus preparation following standard methods and digested with a panel of 16 restriction enzymes following the manufacturer's  
 10 recommendations. Except as noted, all restriction and modifying enzymes were obtained from Boehringer Mannheim, Indianapolis, IN. Genomic DNA was digested with BamHI, PstI, Sall, HindIII or XbaI and the fragments were subcloned into plasmids (K. L. Berkner and P.A. Sharp, *Nucl. Acids Res.*, 11:6003-20 (1983)). After deproteination, synthetic 10bp PacI linkers (New England Biolabs, Beverly, MA) were double digested with PacI and  
 15 BamHI, or PstI.

The PstI, BamHI and HindIII clones generated from C68 are illustrated in Figure 1, parts C, D and E, respectively. The fragments indicated by the shaded boxes were not cloned, but the sequence of the entire genome has been determined through sequencing overlapping clones and viral DNA directly (unshaded boxes). The cloned fragments and insert sizes are  
 20 described in Table 1. In the following table, pBS = pBluescript SK+ clone; pNEB = pNEB 193 clone; pBR = pBR322 clone; No prefix = fragment not cloned

**Table 1. C68 plasmid clones and insert sizes**

Construct Name	Insert Size (base pairs)	Fragment 5' End	Fragment 3' End	5' End Map Unit	3' End Map Unit
<b>Pst-I Fragments</b>					
C68-Pst-A	6768	24784	31551	67.9%	86.4%
pBS:C68-Pst-B	6713	4838	11550	13.2%	31.6%
pBS:C68-Pst-C	5228	14811	20038	40.6%	54.9%
pBS:C68-Pst-D	2739	12072	14810	33.1%	40.6%
pBS:C68-Pst-E	2647	20039	22685	54.9%	32.1%
pBS:C68-Pst-F	1951	32046	33996	87.8%	93.1%
pNEB:C68-Pst-G	1874	1	1874	0.0%	5.1%
pBS:C68-Pst-H	1690	23094	24783	63.2%	67.9%
pBS:C68-Pst-I	1343	33997	35339	93.1%	96.8%
pNEB:C68-Pst-J	1180	35340	36519	96.8%	100.0%
pBS:C68-Pst-K	1111	2763	3873	7.6%	10.6%
pBS:C68-Pst-L	964	3874	4837	10.6%	13.2%
pBS:C68-Pst-M	888	1875	2762	5.1%	7.6%
pBS:C68-Pst-N	408	22686	23093	62.1%	63.2%
C68-Pst-O	380	31666	32045	86.7%	87.7%
pBS:C68-Pst-P	285	11551	11835	31.6%	32.4%
C68-Pst-Q	236	11836	12071	32.4%	33.1%
pBS:C68-Pst-R	114	31552	31665	86.4%	86.7%
<b>BamHI Fragments</b>					
C68-Bam-A	16684	19836	36519	54.3%	100.0%
pBS:C68-Bam-B	8858	3582	12439	9.8%	34.1%
pBS:C68-Bam-C	4410	12440	16849	34.1%	46.1%
pBS:C68-Bam-D	2986	16850	19835	46.1%	54.3%
pNEB:C68-Bam-E	2041	1	2041	0.0%	5.6%
pBS:C68-Bam-F	1540	2042	3581	5.6%	9.8%
<b>HindIII Fragments</b>					
pBR:C68-Hind-B	9150	23471	32620	64.3%	89.3%

Chimpanzee adenovirus, C68, was obtained from ATCC and propagated in human 293 cells. Viral genomic DNA was isolated from purified virions using established procedures (A. R. Davis, *et al.*, *Gene Thera.*, **5**:1148-1152 (1998)) and digested with a panel of restriction enzymes; the data were consistent with previous studies (data not shown) (G. R. Kitchingman, *Gene*, **20**:205-210 (1982); Q. Li and G. Wadell, *Arch Virol.* **101**:65-77 (1998); R. Wigand, *et al.*, *Intervirology.* **30**:1-9 (1989)). Restriction fragments spanning the entire genome of C68 were subcloned into plasmids. A schematic drawing of the C68 genome is shown in Figure 1A, and the Pst-I, BamHI and HindIII fragments that were cloned into plasmid vectors are indicated by the unshaded boxes, in Figs. 1B, 1C, and 1D, respectively.

The cloned fragments, fragment sizes and genomic position are also listed in Table 1. Both plasmid clones and genomic DNA were used as templates for sequencing. The genome was sequenced by primer walking in both directions and each base was included in an average of approximately four reactions.

The C68 genome is 36521 bp in length [see, US Patent 6,083,716]. Preliminary comparison with GenBank sequences indicated varying degrees of similarity with other human and animal adenoviruses along the entire length of the viral genome. Regions with homology to all of the previously described adenoviral genetic units, early regions 1-4 and the major late genes, were found in the C68 genome (Fig. 1A). DNA homology between C68 and the human adenoviruses that have been completely sequenced, Ad2 (NC001405), Ad5 (NC001405), Ad12 (NC001460), Ad17 (NC002067) and Ad40 (NC01464), was used to order the clones. The open reading frames (ORF) were determined and the genes were identified based on homology to other human adenoviruses. All of the major adenoviral early and late genes are present in C68. The inverted terminal repeats (ITR=s) are 130 bp in length.

#### Example 4 - Analysis of C68 sequence

The complete nucleotide sequence of every member of the Mastadenovirus genus accessible from GenBank, including isolates from different species, were screened for identity to C68. The Ad4 minigenome was assembled from the following GenBank sequences: Left-hand ITR (J01964); E1A region (M14918); DNA pol and pTP (X74508, 74672); VA RNA-I, II (U10682); 52, 55K (U52535); pVII (U70921); hexon (X84646);

endoprotease (M16692); DNA-binding protein (M12407); fiber (X76547); right-hand ITR (J01965). The Ad7 composite genome was created from the following sequence data: Mu 3-21 (X03000); VA RNA-I, II, pTP & 52, 55K (U52574); penton (AD001675); pVI, hexon and endoprotease (AF065065); DNA-binding protein (K02530); E3 and fiber region (AF104384);  
5 right-hand ITR (V00037).

The amino acid sequence alignment was generated with Clustal X, edited with Jalview (<http://www.ebi.ac.uk/~michele/jalview/>), and analyzed with Boxshade ([http://www.ch.embnet.org/software/BOX\\_form.html](http://www.ch.embnet.org/software/BOX_form.html)). Publicly available hexon protein sequences from all human adenovirus serotypes were initially aligned to identify the set  
10 showing the highest homology to C68.

The nucleotide sequence and predicted amino acid sequences of all significant open reading frames in the C68 genome were compared to known DNA and protein sequences. The nucleotide sequence of C68 was compared to sequences of Ad 2, 4, 5, 7, 12, 17 and 40. In agreement with previous restriction analysis (Kitchingman, cited above) C68 is most  
15 similar to human Ad4 (subgroup E).

The E1A region of C68 extends from the TATA box at nt 480 to the poly A addition site at 1521. The consensus splice donor and acceptor sites are in the analogous position of the human Ad counterparts, and the 28.2K and 24.8K proteins are similar in size to the human Ad proteins. The ORF for the smallest E1A protein of C68 is predicted to encode 101  
20 residues as opposed to approximately 60 amino acids for other adenoviruses. There is a TTA codon at residue 60 for C68 where other adenoviruses often have a TGA stop codon. The first 60 residues of C68 E1A 100R protein have 85% identity to the Ad4 homolog.

The C68 genome encodes genes for the four E1B proteins, 20.5K, 54.7K, 10.1K and 18.5K as well as pIX. All five C68 encoded proteins are similar in size to that of other Ad  
25 E1B and pIX proteins. The Ad4 homolog of the E1B 21K protein has only 142 amino acids, where C68 has 186 residues and other human adenoviruses have 163-178 residues. The C68 and Ad4 proteins share 95% identity over the first 134 aa, then the similarity ends and the Ad4 protein terminates at 142 amino acids.

The C68 genome encodes homologs of the E2A 55K DNA binding protein and the  
30 Iva2 maturation protein, as well as the E2B terminal protein and the DNA polymerase. All of

the E2 region proteins are similar in size to their human Ad counterparts, and the E2B proteins are particularly well conserved. The C68 E2B 123.6K DNA polymerase is predicted to be 1124 residues, while Ad4 is predicted to have 1193 although the other human adenoviruses have smaller polymerases. Residues 1-71 of the Ad4 polymerase have no  
5 similarity to any other Ad polymerase, and it is possible that this protein actually initiates at an internal ATG codon. From amino acids 72-1193, Ad4 and C68 polymerases have 96% amino acid identity.

The E3 regions of human adenoviruses sequenced so far exhibit considerable sequence and coding capacity variability. Ad40 has five E3 region genes, Ad12 has six, C68  
10 and Ad5 have seven, Ad38 has eight and Ad3 as well as Ad7 (subgroup B human adenoviruses) have nine putative E3 region genes. The Ad4 E3 region has not yet been sequenced. In comparison with the E3 region of Ad35, all 7 E3 gene homologs were identified in the C68 genome (C. F. Basler and M.S. Horwitz, *Virology*, **215**: 165-177 (1996)).

15 The C68 E4 region has 6 ORFs and each is homologous to proteins in the human Ad5, 12 and 40 E4 region. The E4 nomenclature is confusing because the ORF2 homologs of C68, Ad12 and Ad40 are approximately 130 residues, while in Ad5 there are two ORFs encoding proteins of 64 and 67 residues with homology, respectively, to the amino and carboxy terminal ends of the larger ORF2 proteins. ORF5 has been omitted in our nomenclature  
20 because the 5<sup>th</sup> ORF in the E4 region is homologous to the widely studied ORF6 protein of human Ad5.

The major late promoter and the tri-partite leader sequences of the C68 genome were located. ORFs with the potential to encode the 15 major late proteins were located. All of the C68 late proteins are similar in size to their human Ad counterparts. The percent amino  
25 acid identity between chimpanzee and human Ad late proteins varies considerably. The C68 fiber protein is predicted to have 90% amino acid identity with the Ad4 protein, but much less similarity to the other human Ad fiber proteins. The CAR binding site in the fiber knob is present in C68.

### Example 5 - Virus neutralizing antibody assays

Several studies were performed to determine if there is cross-reactivity between type specific antisera of C68 and human adenovirus. The neutralizing activity of sera was tested as follows. Panels of sera from normal human subjects (N=50), rhesus monkeys (N=52) and chimpanzees (N=20) were evaluated for neutralizing antibodies against Ad5 and C68 based vectors using 293 cells as an indicator cell line. Sera collected from individual humans, rhesus monkeys, or chimpanzees were inactivated at 56 °C for 30 minutes. A serial dilution of each sample (1:10, 1:20, 1:40, 1:80, 1:160, 1:320 in 100 µl of DMEM containing 10% FCS) was added to equal amounts of H5.010CMVEGFP (1000 PFU/well) or C68CMVEGFP virus and incubated at 4 °C for two hrs. One hundred and fifty microliters of the mixture were transferred onto 2 x 10<sup>5</sup> 293 cells in 96 well flat bottom plates. Control wells were infected with equal amounts of virus (without addition of serum). Samples were incubated at 37 °C in 5% CO<sub>2</sub> for 48 hrs and examined under a fluorescent microscope. Sample dilutions that showed >50% reduction of green-fluorescent foci as compared to infected controls were scored positive for neutralizing antibodies.

As expected, approximately 35% of normal human subjects demonstrated neutralizing antibody against Ad5, a frequency much higher than observed in sera of rhesus monkeys and chimpanzee. Neutralizing antibody to C68 was observed in 80% of chimpanzee and only 2% of normal human subjects or rhesus monkeys. Titers of neutralizing antibodies in the non-target species were generally low.

To further evaluate cross-reactivity of C68 with human adenovirus vectors, mice were immunized with 2 x 10<sup>7</sup> plaque forming units (pfu) of Ad 2, 4, 5, 7 and 12 as well as C68. Sera were harvested 2 weeks later and tested for antibodies that neutralized either Ad5 or C68 vectors. Neutralizing antibody to Ad5 vector was only detected in animals immunized with Ad5. Importantly, the only animals with neutralizing antibody to C68 vector were those immunized with C68 vector; none of the human serotypes tested, including Ad4, generated antibodies in mice that neutralized C68 *in vitro*.

Important to the utility of C68 vector in human trials is the absence of neutralizing antibody in the human population. In our study, a screen of 50 normal human subjects failed to detect any significant neutralizing antibodies (>1:10) using the same assay that showed

neutralizing antibodies in >50% of chimpanzees. Furthermore, sera of mice immunized with multiple human Ad serotypes including Ad4, did not neutralize infection with C68.

#### Example 6 - Structural analysis of hexon proteins

5       The absence of neutralizing antibodies between C68 and human serotypes compelled us to more carefully evaluate structural differences in the regions of hexon presumed to harbor type specific epitopes. Previous studies have suggested that these epitopes are located within the 7 hypervariable regions of hexon determined by Crawford-Mikszs and Schnurr (*J. Virol*, 70:1836-1844 (1996)). A comparison of the amino acid sequences of hexon proteins  
10       between C68 and several human adenoviruses is shown in Figure 3. Indeed, C68 is substantially dissimilar in significant regions of these hypervariable sequences.

#### Example 7 - Construction of C68-Derived Capsid Containing a Human Fiber Gene

15       To generate a C68-derived vector with an altered tropism, the chimeric fiber gene construct containing the Ad5 fiber knob fused to the C68 tail and shaft is incorporated into a plasmid carrying the C68 genome. For the precise replacement of the wild-type C68 fiber gene, a plasmid carrying the green fluorescent protein driven by a CMV promoter is used for modification of C68 fiber. The resulting transfer vector contains a CMV promoter driven  
20       green fluorescent protein (GFP) expression cassette inserted into the E3 region, the chimeric C68/Ad5 fiber gene, and E4. This transfer vector was used for incorporation of GFP cassette and modified fiber gene into the backbone of an E3 deleted C68 infectious plasmid via homologous recombination in *E. coli*. The viral genome was released from the plasmid by PacI digestion and used to transfect 293 cells. The chimeric C68-derived virus is produced  
25       about 3 weeks following transfection using techniques described herein. Similar techniques can be readily utilized to construct other C68-derived capsids.

      All publications cited in this specification are incorporated herein by reference. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from  
30       the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

What is claimed is:

1. A C68 chimpanzee adenoviral capsid protein which is substantially free of other viral proteins with which it is naturally associated, said protein selected from the group consisting of:

(a) a hexon protein characterized by the amino acid sequence of SEQ ID NO:17;

(b) a penton protein characterized by the amino acid sequence of SEQ ID NO:12;

(c) a fiber protein characterized by the amino acid sequence of SEQ ID NO:27;

(d) a unique fragment of any of (a) to (c) comprising 8 amino acid residues in length.

2. The C68 chimpanzee adenoviral capsid protein according to claim 1, wherein the fragment of hexon protein (a) is selected from the group consisting of:

(i) about amino acids 125 to 443 of SEQ ID NO:16;

(ii) about amino acids 131 to about 441 of SEQ ID NO:16;

(iii) about amino acids 138 to about 441 of SEQ ID NO:16;

(iv) about amino acids 138 to about 163 of SEQ ID NO:16;

(v) about amino acids 170 to about 176 of SEQ ID NO:16;

(vi) about amino acids 195 to about 203 of SEQ ID NO:16;

(vii) about amino acids 233 to about 246 of SEQ ID NO:16;

(viii) about amino acids 253 to about 264 of SEQ ID NO:16;

(ix) about amino acids 287 to about 297 of SEQ ID NO:16; and

(x) about amino acids 404 to about 430 of SEQ ID NO:16.

3. The C68 chimpanzee adenoviral capsid protein according to claim 1, wherein the fragment of fiber protein (c) is about amino acids 247 to 425 of SEQ ID NO:27.



4. A novel adenovirus serotype comprising a unique fragment of the C68 hexon protein according to claim 1 fused to a heterologous adenovirus hexon peptide.

5. The novel adenovirus serotype according to claim 4, wherein said fragment is selected from the group consisting of:

- (a) about amino acids 125 to about 443 of SEQ ID NO:16;
- (b) about amino acids 131 to about 441 of SEQ ID NO:16;
- (c) about amino acids 138 to about 441 of SEQ ID NO:16;
- (d) about amino acids 138 to about 163 of SEQ ID NO:16;
- (e) about amino acids 170 to about 176 of SEQ ID NO:16;
- (f) about amino acids 195 to about 203 of SEQ ID NO:16;
- (g) about amino acids 233 to about 246 of SEQ ID NO:16;
- (h) about amino acids 253 to about 264 of SEQ ID NO:16;
- (i) about amino acids 287 to about 297 of SEQ ID NO:16; and
- (j) about amino acids 404 to about 430 of SEQ ID NO:16.

6. The novel adenovirus serotype according to claim 4, wherein the C68 fragment is a loop region of the hexon.

7. The novel adenovirus serotype according to claim 4, wherein at least one loop region of the C68 hexon protein is substituted with a loop region from a heterologous adenovirus serotype.

8. A recombinant adenovirus comprising a capsid of the novel adenovirus serotype of any of claims 2 to 7 encapsidating a molecule for delivery to a target cell.

9. The recombinant virus according to claim 8, wherein the molecule comprises an adenovirus 5' inverted terminal repeat sequence (ITRs), a minigene, and an adenovirus 3' ITR.

10. The recombinant adenovirus according to claim 9, wherein the adenovirus ITRs are from a serotype heterologous to C68.
11. An adenoviral capsid comprising a C68 capsid protein according to claim 1 and a protein from a heterologous adenoviral capsid protein.
12. The adenoviral capsid according to claim 11, wherein the capsid comprises the C68 hexon and at least the penton or the fiber is from a different adenovirus serotype.
13. The adenoviral capsid according to claim 12, wherein the penton and fiber are from a human adenovirus serotype.
14. The adenoviral capsid according to claim 12, wherein the penton is from C68 and the fiber is from a different adenovirus serotype.
15. The adenoviral capsid according to claim 12, wherein the fiber is from C68 and the penton is from a different adenovirus serotype.
16. The adenoviral capsid according to claim 11, wherein the C68 protein is selected from the penton and the fiber and the hexon is from a different adenovirus serotype.
17. A recombinant adenovirus comprising an adenoviral capsid according to any of claims 11 to 16, said capsid encapsidating a molecule for delivery to a target cell.
18. A pharmaceutical composition comprising a physiologically acceptable carrier and a recombinant virus according to claim 17.
19. Use of a recombinant adenovirus according to claim 8 or claim 17 for delivering a molecule to a target cell.
20. Use according to claim 19, wherein said molecule is an immunogen.

21. Use according to claim 19, wherein said molecule is a therapeutic molecule.
22. A pseudotyped adenovirus comprising a C68 adenoviral capsid having an amino acid sequence as provided in SEQ ID NO:16 encapsidating a molecule comprising adenovirus 5' inverted terminal repeat sequences (ITR), a minigene, and adenovirus 3' ITR, wherein each of the 5' and 3' ITRs are from a serotype heterologous to C68.
23. A pharmaceutical composition comprising a physiologically acceptable carrier and a pseudotyped adenovirus according to claim 22.
24. Use of a pseudotyped adenovirus according to claim 22 for delivering a molecule to a target cell.
25. Use according to claim 22, wherein said molecule is an immunogen.
26. Use according to claim 22, wherein said molecule is a therapeutic molecule.
27. A method for rapid screening of recombinant constructs comprising the steps of:
  - (a) providing a first parent construct having a green fluorescent protein (GFP), operably linked to regulatory sequences which permit its expression in a host cell, downstream of the portion of the first parent construct to be in the recombinant construct;
  - (b) providing a second parent construct having a GFP operably linked to regulatory sequences which permit its expression in a host cell upstream of the portion of the second parent construct to be in the recombinant construct;
  - (c) culturing a selected host cell with the first parent construct and second parent construct under conditions which permits them to homologously recombine; and
  - (d) screening for the absence expression of GFP expression, which indicates the presence of the recombinant construct.

28. The method according to claim 27, wherein the regulatory sequence comprises the prokaryotic promoter from lacZ.

29. The method according to claim 27, wherein the first parent construct is a plasmid.

30. The method according to claim 27, wherein the second parent constructs is a plasmid.

31. The method according to claim 27, wherein the first parent construct and the second parent construct are provided by co-transfection into the cell.

32. The method according to claim 27, wherein one of the first parent construct or the second parent construct is stably contained within the host cell.

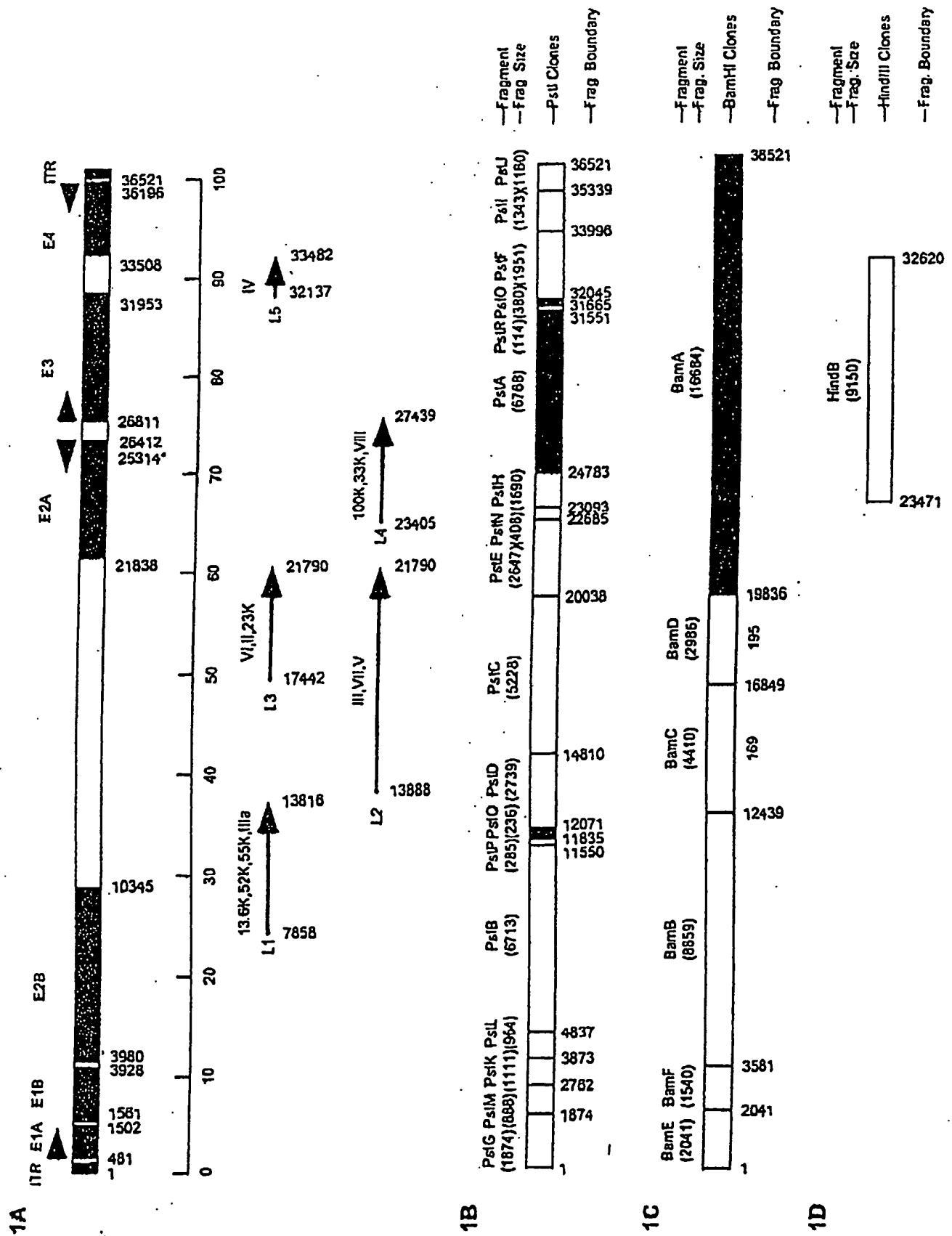
33. A host cell comprising:

- (a) a first parent construct having a green fluorescent protein (GFP), operably linked to regulatory sequences which permit its expression in a host cell, downstream of the portion of the first parent construct to be in the recombinant construct; and
- (b) a second parent construct having a GFP operably linked to regulatory sequences which permit its expression in a host cell upstream of the portion of the second parent construct to be in the recombinant construct.

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FIG. 1



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FIG. 2

C68 - E 130	NTCQWTKADGETA-TE	NTCQWTKADGETA-TE	KTYTYGNAPVQGIN	ITKDGIOGLGTD-T	DDOPI
Ad4 - E 130	NTCQW--K-DSBS	NTCQW--K-DSBS	KMHT--CAAAAPCVTGKKIEADGIP	IRIDSTS--	GTDTVI
Ad16 - E 130	NTCQW--K-DSBS	NTCQW--K-DSBS	KMHT--GVAAMPCTGKKIEADGIP	GIDSTS--	GTDTVI
Ad3 - B 130	NTSQWIVTTINGDNAVTT	NTSQWIVTTINGDNAVTT	TTNT--CIASMKCN	ITK--GLGCKDIT	TTEGEEKPI
Ad7 - B 130	NTSQWIVTAGEERAVTT	NTSQWIVTAGEERAVTT	TTNT--CIASMKCN	ITK--GLGCKDIT	--ADNKPI
Ad2 - C 130	NSCEMEQTEDSGRAVAE	NSCEMEQTEDSGRAVAE	DEEEEEEEQNARDQATKTHVACAP	SCET--	ITKSGIOIG--SDNAETQA--KP
C68 - E 177	YADKTYQPEPQVGDAEWH	YADKTYQPEPQVGDAEWH	ITGTDEKYGGRALKPD	TKMKPCYGSFAKPTNKEGGQA	N--VK--TGTC--TTKEYDIDMAF
Ad4 - E 177	YADKTYQPEPQVGNDSW	YADKTYQPEPQVGNDSW	VDNCAE--EKYGGRALKDT	TKMNPCYGSFAKPTNKEGGQA	N--K--DSEP--ATTPNVYDIDAF
Ad16 - E 177	YADKTYQPEPQVGNASW	YADKTYQPEPQVGNASW	VDNCAE--EKYGGRALKDT	TKMNPCYGSFAKPTNKEGGQA	N--K--DSEP--ATTPNVYDIDAF
Ad3 - B 183	YADKTYQPEPQVGESW	YADKTYQPEPQVGESW	TDGTE--EKYGGRALKPD	TKMKPCYGSFAKPTNKEGGQA	N--K--DSEP--ATTPNVYDIDAF
Ad7 - B 181	YADKTYQPEPQVGESW	YADKTYQPEPQVGESW	TDGTE--EKYGGRALKPD	TKMKPCYGSFAKPTNKEGGQA	N--K--DSEP--ATTPNVYDIDAF
Ad2 - C 205	YADPSYQPEPQIGESQW	YADPSYQPEPQIGESQW	NEADA--N--AAGGRVLKKT	TPMKPCYGSFAKPTNPFGGQ	S--V--VPD--EKGV--PLPKVDIQF
C68 - E 251	FDNRSAA	FDNRSAA	AAGLAPEI	VLYTENVDLETPDTHIVYKAGT	DDSSSINLQQQAMPNRPNYIGFRDNF
Ad4 - E 253	FDSKII	FDSKII	IVMYTENVDLETPDTHIVYKPGT	DDSSSINLQQQAMPNRPNYIGFRDNF	FGLMYYNSTGNN
Ad16 - E 253	FDNKNI	FDNKNI	IVMYTENVDLETPDTHIVYKPGT	DDSSSINLQQQAMPNRPNYIGFRDNF	FGLMYYNSTGNN
Ad3 - B 259	FDGRDAV	FDGRDAV	AGLAPEI	VLYTENVDLETPDTHIVYKPGT	DDSSSINLQQQAMPNRPNYIGFRDNF
Ad7 - B 130	FDGREB	FDGREB	ADAFPEI	VLYTENVDLETPDTHIVYKPGT	DDSSSINLQQQAMPNRPNYIGFRDNF
Ad2 - C 277	FSNTISLNDROQNA	FSNTISLNDROQNA	TKPKVLYSE	EDVNTETPDTHISYKPKG	GDENSKAMLGQQSMPNRPNYIGFRDNF
C68 - E 327	GVLAGQASQLNAVVDLQDR	GVLAGQASQLNAVVDLQDR	NTELSYQ	LLDLSLGDRTTRYFSMW	NQAVDSYDPDVRITENHGV
Ad4 - E 328	GVLAGQASQLNAVVDLQDR	GVLAGQASQLNAVVDLQDR	NTELSYQ	LLDLSLGDRTTRYFSMW	NQAVDSYDPDVRITENHGV
Ad16 - E 328	GVLAGQASQLNAVVDLQDR	GVLAGQASQLNAVVDLQDR	NTELSYQ	LLDLSLGDRTTRYFSMW	NQAVDSYDPDVRITENHGV
Ad3 - B 338	GVLAGQASQLNAVVDLQDR	GVLAGQASQLNAVVDLQDR	NTELSYQ	LLDLSLGDRTTRYFSMW	NQAVDSYDPDVRITENHGV
Ad7 - B 334	GVLAGQASQLNAVVDLQDR	GVLAGQASQLNAVVDLQDR	NTELSYQ	LLDLSLGDRTTRYFSMW	NQAVDSYDPDVRITENHGV
Ad2 - C 357	GVLAGQASQLNAVVDLQDR	GVLAGQASQLNAVVDLQDR	NTELSYQ	LLDLSLGDRTTRYFSMW	NQAVDSYDPDVRITENHGV
C68 - E 407	YQGIKANG	YQGIKANG	-----T-----	DOTTWTKDDS	VNDANEIGKGNPFAM
Ad4 - E 408	YQGIKVKTD	YQGIKVKTD	--AG-S--	-----KWDKDD	TVSMANEIHVGNPFAM
Ad16 - E 408	YQGIKVKTD	YQGIKVKTD	AVAGTSG	-----TQWDKDD	TVSTANEIHGCGNPFAM
Ad3 - B 418	YQGIKVKTD	YQGIKVKTD	-----	DTNGMEKDN	VAPANEITIGNNIFAM
Ad7 - B 414	YQGIKVK	YQGIKVK	-----	D--NGMEKDDN	VSKONEIIGNNQAM
Ad2 - C 437	YQGIKANGS-GDNGD	YQGIKANGS-GDNGD	-----TTWTKD	-----FATRNEIGVGNPFAM	

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FIG. 3

Pan-9 fiber knob	(1)	TLWTPDPSPNCQILAENDAKLTLCLTKCGSQILATVSVLVGSG-NLNP
Ad 2 fiber knob	(1)	TLWTPDPSPNCRIHSDNDCKFTLVLTCKGSQVLATVAALAVSG--DLSS
Ad 5 fiber knob	(1)	TLWTPAPSPNCRNLNAEKDAKLTLLVLTCKGSQILATVSVLAVKG--SLAP
Pan-9 fiber knob	(50)	ITGTVSSAQVFLRFDANGVLLTEHSTLKKYWGYRQGDSIDGTPYTNAVGF
Ad 2 fiber knob	(49)	MTGTVASVSIFLRFDQNGVLMENSSSLKKHYWNFRNGNSTNANPYTNAVGF
Ad 5 fiber knob	(49)	ISGTVQSAHLIIRFDENGVLNNSFLDPEYWNFRNGDLTEGTAYTNAVGF
Pan-9 fiber knob	(100)	MPNLKAYPKSQSSTTKNNIVGQVYMNMGDVSKPMLLTITLNGTDDS-----
Ad 2 fiber knob	(99)	MPNLLAYPKTSQTAKNNIVSQVYLHGDKTKPMLTITLNGTSESTETSE
Ad 5 fiber knob	(99)	MPNLSAYPKSHGKTAKSNIVSQVYLNMGDKTKPVTTLTITLNGTQET-GDTT
Pan-9 fiber knob	(145)	NSTYSMSFSYTW-T-NGSYVVGATFGANSYTFFSYIAQE
Ad 2 fiber knob	(149)	VSTYSMSFTWSWE-SGKYTTETTFATNSYTFFSYIAQE
Ad 5 fiber knob	(148)	PSAYSMSFSWDWS-GHNYINEIFATSSYTFFSYIAQE

Hu5 Pan-9	APKGAPNPCEWDEAAATALEINLEEEDDDNEDEVDEQAEEQKTHVFGQAPYSGINITKEGIQIGVEGQT-- APKGAPNTCQWTYKADG-----ETATEKTYTYGNAPVQGINITKDGIGLGTDTDD--
Hu5 Pan-9	--PKYADKTFQPEPQIGESQWYETEIN--HAAGRVLKKTTPMKPCYGSYAKPTNENGGQGILVKQQN--G -QPIYADKTYQPEPQVGVGDAEWHDITGTDEKYGGRALKPDTKMKPCYGSFAKPTNKEGGQANVKTGTG--T
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Hu5 Pan-9	IAFRDNFIGLMYYNSTGNMGVLAGQASQLNAVVDLQDRNTELSYQLLLDSIGDRTRYFSMWNQAVDSYDP IGFRDNFIGLMYYNSTGNMGVLAGQASQLNAVVDLQDRNTELSYQLLLDSIGDRTRYFSMWNQAVDSYDP
Hu5 Pan-9	DVRIIENHGTEDELPNYCFPLGGVINTETLTKVKPKTG-----QENGWEKDATEFSDKNEIRVGNNFAMEI DVRIIENHGVEDELPNYCFPLDAVGRTDTYQGIKAN-----GTDQTTWTKKDDSVN-DANEIGKGNPFAMEI

FIG. 4



## SEQUENCE LISTING

<110> The Trustees of the University of Pennsylvania  
Gao, Guangping  
Wilson, James M.

<120> Method for Rapid Screening of Bacterial Transformants and  
Novel Simian Adenovirus Proteins

<130> UPN-N2630PCT

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Lys Ile Leu Arg Tyr Asp Glu Ser Lys Thr Arg Cys Arg Ala Cys Glu
          115          120          125

Cys Gly Gly Lys His Ala Arg Phe Gln Pro Val Cys Val Asp Val Thr
          130          135          140

Glu Asp Leu Arg Pro Asp His Leu Val Leu Pro Cys Thr Gly Thr Glu
145          150          155          160

Phe Gly Ser Ser Gly Glu Glu Ser Asp
          165

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 <213> chimpanzee C68 adenovirus protein

<400> 7

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Met Glu Ser Arg Asn Pro Phe Gln Gln Gly Leu Pro Ala Gly Phe Leu
1          5          10          15

Ser Ser Ser Phe Val Glu Asn Met Glu Val Pro Ala Pro Glu Cys Asn
          20          25          30

Leu Arg Leu Leu Ala Gly Thr Ala Ala Arg His Ser Glu Asp Pro Glu
          35          40          45

Ser Pro Gly Glu Ser Gln Gly Thr Pro Thr Ser Pro Ala Ala Ala Ala
          50          55          60

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Gly Gly Gly Ser Arg Arg Glu Pro Glu Ser Arg Pro Gly Pro Ser Gly  
65 70 75 80

Gly Gly Gly Gly Val Ala Asp Leu Pro Cys Val Trp Met  
85 90

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<213> chimpanzee C68 adenovirus protein

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Met Ser Gly Ser Gly Ser Phe Glu Gly Gly Val Phe Ser Pro Tyr Leu  
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Thr Gly Arg Leu Pro Ser Trp Ala Gly Val Arg Gln Asn Val Met Gly  
20 25 30

Ser Thr Val Asp Gly Arg Pro Val Gln Pro Ala Asn Ser Ser Thr Leu  
35 40 45

Thr Tyr Ala Thr Leu Ser Ser Ser Ser Leu Asp Ala Ala Ala Ala Ala  
50 55 60

Ala Ala Ala Ser Ala Ala Ser Ala Val Arg Gly Met Ala Met Gly Ala  
65 70 75 80

Gly Tyr Tyr Gly Thr Leu Val Ala Asn Ser Ser Ser Thr Asn Asn Pro  
85 90 95

Ala Ser Leu Asn Glu Glu Lys Leu Leu Leu Leu Met Ala Gln Leu Glu  
100 105 110

Ala Leu Thr Gln Arg Leu Gly Glu Leu Thr Gln Gln Val Ala Gln Leu  
115 120 125

Gln Glu Gln Thr Arg Ala Ala Val Ala Thr Val Lys Ser Lys  
130 135 140

<210> 9  
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<212> PRT  
<213> chimpanzee C68 adenovirus protein

<400> 9

Met Glu Thr Lys Gly Arg Arg Ser Gly Ala Val Phe Asp Gln Pro Asp  
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Glu Pro Glu Ala His Pro Arg Lys Arg Pro Ala Arg Arg Ala Pro Leu  
20 25 30

His Arg Asp Gly Asp His Pro Asp Ala Asp Ala Ala Thr Leu Glu Gly  
35 40 45

Pro Asp Pro Gly Cys Ala Gly Arg Pro Ser Ser Gly Ala Ile Leu Pro  
50 55 60

Gln Pro Ser Gln Pro Ala Lys Arg Gly Gly Leu Leu Asp Arg Asp Ala  
 65 70 75 80  
 Val Glu His Ile Thr Glu Leu Trp Asp Arg Leu Glu Leu Leu Gln Gln  
 85 90 95  
 Thr Leu Ser Lys Met Pro Met Ala Asp Gly Leu Lys Pro Leu Lys Asn  
 100 105 110  
 Phe Ala Ser Leu Gln Glu Leu Leu Ser Leu Gly Gly Glu Arg Leu Leu  
 115 120 125  
 Ala Glu Leu Val Arg Glu Asn Met His Val Arg Glu Met Met Asn Glu  
 130 135 140  
 Val Ala Pro Leu Leu Arg Glu Asp Gly Ser Cys Leu Ser Leu Asn Tyr  
 145 150 155 160  
 His Leu Gln Pro Val Ile Gly Val Ile Tyr Gly Pro Thr Gly Cys Gly  
 165 170 175  
 Lys Ser Gln Leu Leu Arg Asn Leu Leu Ser Ala Gln Leu Ile Ser Pro  
 180 185 190  
 Ala Pro Glu Thr Val Phe Phe Ile Ala Pro Gln Val Asp Met Ile Pro  
 195 200 205  
 Pro Ser Glu Leu Lys Ala Trp Glu Met Gln Ile Cys Glu Gly Asn Tyr  
 210 215 220  
 Ala Pro Gly Ile Glu Gly Thr Phe Val Pro Gln Ser Gly Thr Leu Arg  
 225 230 235 240  
 Pro Lys Phe Ile Lys Met Ala Tyr Asp Asp Leu Thr Gln Asp His Asn  
 245 250 255  
 Tyr Asp Val Ser Asp Pro Arg Asn Val Phe Ala Gln Ala Ala Ala His  
 260 265 270  
 Gly Pro Ile Ala Ile Ile Met Asp Glu Cys Met Glu Asn Leu Gly Gly  
 275 280 285  
 His Lys Gly Val Ala Lys Phe Phe His Ala Phe Pro Ser Lys Leu His  
 290 295 300  
 Asp Lys Phe Pro Lys Cys Thr Gly Tyr Thr Val Leu Val Val Leu His  
 305 310 315 320  
 Asn Met Asn Pro Arg Arg Asp Leu Gly Gly Asn Ile Ala Asn Leu Lys  
 325 330 335  
 Ile Gln Ala Lys Met His Leu Ile Ser Pro Arg Met His Pro Ser Gln  
 340 345 350  
 Leu Asn Arg Phe Val Asn Thr Tyr Thr Lys Gly Leu Pro Val Ala Ile  
 355 360 365  
 Ser Leu Leu Leu Lys Asp Ile Val Gln His His Ala Leu Arg Pro Cys  
 370 375 380  
 Tyr Asp Trp Val Ile Tyr Asn Thr Thr Pro Glu His Glu Ala Leu Gln  
 385 390 395 400



Trp Ser Tyr Leu His Pro Arg Asp Gly Leu Met Pro Met Tyr Leu Asn  
405 410 415

Ile Gln Ala His Leu Tyr Arg Val Leu Glu Lys Ile His Arg Val Leu  
420 425 430

Asn Asp Arg Asp Arg Trp Ser Arg Ala Tyr Arg Ala Arg Lys Ile Lys  
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Met Ala Val Asp Val Met Glu Val Glu Met Pro Thr Ala Arg Arg Thr  
20 25 30

Leu Val Leu Val Phe Ile Gln Ala Ala Thr Val Leu Ala Thr Leu His  
35 40 45

Gly Met His Val Leu His Glu Leu Tyr Leu Ser Ser Phe Asp Glu Glu  
50 55 60

Phe Gln Trp Glu Val Glu Ser Trp Arg Leu His Leu Val Leu Tyr Tyr  
65 70 75 80

Val Val Val Val Gly Leu Ala Leu Phe Cys Leu Asp Gly Gly His Ala  
85 90 95

Asp Glu Pro Ala Arg Glu Ala Gly Pro Asp Leu Gly Ala Ser Gly Ser  
100 105 110

Glu Ser Glu Asp Glu Gly Ala Gln Ala Gly Ala Val Gln Gly Pro Glu  
115 120 125

Thr Leu Arg Ser Gln Val Ser Gly Xaa Arg Arg Arg Ala Val Asp Leu  
130 135 140

Gln Glu Phe Phe Gln Gly Ala Arg Glu Val Xaa Met Val Leu Asp Leu  
145 150 155 160

His Arg Ala Ile Gly Gly Glu Leu His Gly Leu Gln Gly Pro Val Pro  
165 170 175

Leu Gly Cys Asp His Arg Pro Pro Phe Leu Leu Gly Arg Leu Gly Arg  
180 185 190

Arg Gly Arg Cys Leu Phe His Gly  
                   195                  200

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Met	His	Pro	Val	Leu	Arg	Gln	Met	Arg	Pro	His	His	Pro	Pro	Pro	Gln
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Gln	Gln	Pro	Pro	Pro	Gln	Pro	Ala	Leu	Leu	Pro	Pro	Pro	Gln	Gln	Gln
			20					25					30		
Leu	Pro	Ala	Thr	Thr	Ala	Ala	Ala	Ala	Val	Ser	Gly	Ala	Gly	Gln	Ser
		35					40					45			
Tyr	Asp	His	Gln	Leu	Ala	Leu	Glu	Glu	Gly	Glu	Gly	Leu	Ala	Arg	Leu
	50					55					60				
Gly	Ala	Ser	Ser	Pro	Glu	Arg	His	Pro	Arg	Val	Gln	Met	Lys	Arg	Asp
65					70					75				80	
Ala	Arg	Glu	Ala	Tyr	Val	Pro	Lys	Gln	Asn	Leu	Phe	Arg	Asp	Arg	Ser
				85					90					95	
Gly	Glu	Glu	Pro	Glu	Glu	Met	Arg	Ala	Ala	Arg	Phe	His	Ala	Gly	Arg
			100					105					110		
Glu	Leu	Arg	Arg	Gly	Leu	Asp	Arg	Lys	Arg	Val	Leu	Arg	Asp	Glu	Asp
		115					120					125			
Phe	Glu	Ala	Asp	Glu	Leu	Thr	Gly	Ile	Ser	Pro	Ala	Arg	Ala	His	Val
	130					135					140				
Ala	Ala	Ala	Asn	Leu	Val	Thr	Ala	Tyr	Glu	Gln	Thr	Val	Lys	Glu	Glu
145				150						155				160	
Ser	Asn	Phe	Gln	Lys	Ser	Phe	Asn	Asn	His	Val	Arg	Thr	Leu	Ile	Ala
			165						170					175	
Arg	Glu	Glu	Val	Thr	Leu	Gly	Leu	Met	His	Leu	Trp	Asp	Leu	Leu	Glu
			180					185					190		
Ala	Ile	Val	Gln	Asn	Pro	Thr	Ser	Lys	Pro	Leu	Thr	Ala	Gln	Leu	Phe
	195						200					205			
Leu	Val	Val	Gln	His	Ser	Arg	Asp	Asn	Glu	Ala	Phe	Arg	Glu	Ala	Leu
	210					215					220				
Leu	Asn	Ile	Thr	Glu	Pro	Glu	Gly	Arg	Trp	Leu	Leu	Asp	Leu	Val	Asn
225					230					235				240	
Ile	Leu	Gln	Ser	Ile	Val	Val	Gln	Glu	Arg	Gly	Leu	Pro	Leu	Ser	Glu
			245					250						255	
Lys	Leu	Ala	Ala	Ile	Asn	Phe	Ser	Val	Leu	Ser	Leu	Gly	Lys	Tyr	Tyr
		260						265					270		

Ala Arg Lys Ile Tyr Lys Thr Pro Tyr Val Pro Ile Asp Lys Glu Val  
 275 280 285

Lys Ile Asp Gly Phe Tyr Met Arg Met Thr Leu Lys Val Leu Thr Leu  
 290 295 300

Ser Asp Asp Leu Gly Val Tyr Arg Asn Asp Arg Met His Arg Ala Val  
 305 310 315 320

Ser Ala Ser Arg Arg Arg Glu Leu Ser Asp Gln Glu Leu Met His Ser  
 325 330 335

Leu Gln Arg Ala Leu Thr Gly Ala Gly Thr Glu Gly Glu Ser Tyr Phe  
 340 345 350

Asp Met Gly Ala Asp Leu His Trp Gln Pro Ser Arg Arg Ala Leu Glu  
 355 360 365

Ala Ala Ala Gly Pro Tyr Val Glu Glu Val Asp Asp Glu Val Asp Glu  
 370 375 380

Glu Gly Glu Tyr Leu Glu Asp  
 385 390

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Val Met Gln Gln Ala Met Ala Ala Ala Met Gln Pro Pro Leu Glu  
 20 25 30

Ala Pro Tyr Val Pro Pro Arg Tyr Leu Ala Pro Thr Glu Gly Arg Asn  
 35 40 45

Ser Ile Arg Tyr Ser Glu Leu Ala Pro Leu Tyr Asp Thr Thr Arg Leu  
 50 55 60

Tyr Leu Val Asp Asn Lys Ser Ala Asp Ile Ala Ser Leu Asn Tyr Gln  
 65 70 75 80

Asn Asp His Ser Asn Phe Leu Thr Thr Val Val Gln Asn Asn Asp Phe  
 85 90 95

Thr Pro Thr Glu Ala Ser Thr Gln Thr Ile Asn Phe Asp Glu Arg Ser  
 100 105 110

Arg Trp Gly Gly Gln Leu Lys Thr Ile Met His Thr Asn Met Pro Asn  
 115 120 125

Val Asn Glu Phe Met Tyr Ser Asn Lys Phe Lys Ala Arg Val Met Val  
 130 135 140

Ser Arg Lys Thr Pro Asn Gly Val Thr Val Thr Glu Asp Tyr Asp Gly  
 145 150 155 160

Ser Gln Asp Glu Leu Lys Tyr Glu Trp Val Glu Phe Glu Leu Pro Glu  
 165 170 175  
 Gly Asn Phe Ser Val Thr Met Thr Ile Asp Leu Met Asn Asn Ala Ile  
 180 185 190  
 Ile Asp Asn Tyr Leu Ala Val Gly Arg Gln Asn Gly Val Leu Glu Ser  
 195 200 205  
 Asp Ile Gly Val Lys Phe Asp Thr Arg Asn Phe Arg Leu Gly Trp Asp  
 210 215 220  
 Pro Val Thr Glu Leu Val Met Pro Gly Val Tyr Thr Asn Glu Ala Phe  
 225 230 235 240  
 His Pro Asp Ile Val Leu Leu Pro Gly Cys Gly Val Asp Phe Thr Glu  
 245 250 255  
 Ser Arg Leu Ser Asn Leu Leu Gly Ile Arg Lys Arg Gln Pro Phe Gln  
 260 265 270  
 Glu Gly Phe Gln Ile Met Tyr Glu Asp Leu Glu Gly Gly Asn Ile Pro  
 275 280 285  
 Ala Leu Leu Asp Val Asp Ala Tyr Glu Lys Ser Lys Glu Asp Ala Ala  
 290 295 300  
 Ala Glu Ala Thr Ala Ala Val Ala Thr Ala Ser Thr Glu Val Arg Gly  
 305 310 315 320  
 Asp Asn Phe Ala Ser Ala Ala Ala Val Ala Ala Ala Glu Ala Ala Glu  
 325 330 335  
 Thr Glu Ser Lys Ile Val Ile Gln Pro Val Glu Lys Asp Ser Lys Asn  
 340 345 350  
 Arg Ser Tyr Asn Val Leu Pro Asp Lys Ile Asn Thr Ala Tyr Arg Ser  
 355 360 365  
 Trp Tyr Leu Ala Tyr Asn Tyr Gly Asp Pro Glu Lys Gly Val Arg Ser  
 370 375 380  
 Trp Thr Leu Leu Thr Thr Ser Asp Val Thr Cys Gly Val Glu Gln Val  
 385 390 395 400  
 Tyr Trp Ser Leu Pro Asp Met Met Gln Asp Pro Val Thr Phe Arg Ser  
 405 410 415  
 Thr Arg Gln Val Ser Asn Tyr Pro Val Val Gly Ala Glu Leu Leu Pro  
 420 425 430  
 Val Tyr Ser Lys Ser Phe Phe Asn Glu Gln Ala Val Tyr Ser Gln Gln  
 435 440 445  
 Leu Arg Ala Phe Thr Ser Leu Thr His Val Phe Asn Arg Phe Pro Glu  
 450 455 460  
 Asn Gln Ile Leu Val Arg Pro Pro Ala Pro Thr Ile Thr Thr Val Ser  
 465 470 475 480  
 Glu Asn Val Pro Ala Leu Thr Asp His Gly Thr Leu Pro Leu Arg Ser  
 485 490 495

Ser Ile Arg Gly Val Gln Arg Val Thr Val Thr Asp Ala Arg Arg Arg  
                   500                                  505                                  510

Thr Cys Pro Tyr Val Tyr Lys Ala Leu Gly Ile Val Ala Pro Arg Val  
                   515                                  520                                  525

Leu Ser Ser Arg Thr Phe  
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Ala Pro Ser Lys Met Tyr Gly Gly Ala Arg Gln Arg Ser Thr Gln His  
                   20                                  25                                  30

Pro Val Arg Val Arg Gly His Phe Arg Ala Pro Trp Gly Ala Leu Lys  
                   35                                  40                                  45

Gly Arg Val Arg Ser Arg Thr Thr Val Asp Asp Val Ile Asp Gln Val  
           50                                  55                                  60

Val Ala Asp Ala Arg Xaa Tyr Thr Pro Ala Ala Ala Pro Val Ser Thr  
 65                                  70                                  75                                  80

Val Asp Ala Val Ile Asp Ser Val Val Ala Asp Ala Arg Arg Tyr Ala  
                   85                                  90                                  95

Arg Ala Lys Ser Arg Arg Arg Arg Ile Ala Arg Arg His Arg Ser Thr  
                   100                                  105                                  110

Pro Ala Met Arg Ala Ala Arg Ser Leu Val Ala Gln Gly Gln Ala His  
                   115                                  120                                  125

Gly Thr Gln Gly His Val Gln Gly Gly Gln Thr Arg Gly Phe Arg Arg  
           130                                  135                                  140

Gln Arg Arg Gln Asp Pro Glu Thr Arg Gly His Gly Gly Gly Ser Gly  
 145                                  150                                  155                                  160

His Arg Gln His Val Pro Pro Ala Ala Arg Glu Arg Val Leu Gly Ala  
                   165                                  170                                  175

Arg Arg Arg His Arg Cys Ala Arg Ala Arg Ala His Pro Pro Pro Ser  
                   180                                  185                                  190

His Leu Lys Met Phe Thr Ser Arg Cys  
           195                                  200

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Glu	Ile	Tyr	Gly	Pro	Ala	Val	Val	Lys	Glu	Glu	Arg	Lys	Pro	Arg	Lys	20	25	30	
Ile	Lys	Arg	Val	Lys	Lys	Asp	Lys	Lys	Glu	Glu	Glu	Ser	Asp	Val	Asp	35	40	45	
Gly	Leu	Val	Glu	Phe	Val	Arg	Glu	Phe	Ala	Pro	Arg	Arg	Arg	Val	Gln	50	55	60	
Trp	Arg	Gly	Arg	Lys	Val	Gln	Pro	Val	Leu	Arg	Pro	Gly	Thr	Thr	Val	65	70	75	80
Val	Phe	Thr	Pro	Gly	Glu	Arg	Ser	Gly	Thr	Ala	Ser	Lys	Arg	Ser	Tyr	85	90	95	
Asp	Glu	Val	Tyr	Gly	Asp	Asp	Asp	Ile	Leu	Glu	Gln	Ala	Ala	Xaa	Arg	100	105	110	
Leu	Gly	Glu	Phe	Ala	Tyr	Gly	Lys	Arg	Ser	Arg	Ser	Ala	Pro	Lys	Glu	115	120	125	
Glu	Ala	Val	Ser	Ile	Pro	Leu	Asp	His	Gly	Asn	Pro	Thr	Pro	Ser	Leu	130	135	140	
Lys	Pro	Val	Thr	Leu	Gln	Gln	Val	Leu	Pro	Thr	Ala	Ala	Pro	Arg	Arg	145	150	155	160
Gly	Phe	Lys	Arg	Glu	Gly	Glu	Asp	Leu	Tyr	Pro	Thr	Met	Gln	Leu	Met	165	170	175	
Val	Pro	Lys	Arg	Gln	Lys	Xaa	Glu	Asp	Val	Leu	Glu	Thr	Met	Lys	Val	180	185	190	

Asp Pro Asp Val Gln Pro Glu Val Lys Val Arg Pro Ile Lys Gln Val  
 195 200 205  
 Ala Pro Gly Xaa Gly Val Gln Thr Val Asp Ile Xaa Ile Pro Thr Glu  
 210 215 220  
 Pro Met Glu Thr Gln Thr Glu Pro Met Ile Lys Pro Ser Thr Ser Thr  
 225 230 235 240  
 Met Glu Val Gln Thr Asp Pro Trp Met Pro Ser Ala Pro Ser Arg Arg  
 245 250 255  
 Pro Arg Arg Lys Tyr Gly Ala Ala Ser Leu Leu Met Pro Asn Tyr Ala  
 260 265 270  
 Leu His Pro Ser Ile Ile Pro Thr Pro Gly Tyr Arg Gly Thr Arg Phe  
 275 280 285  
 Tyr Arg Gly His Thr Ser Ser Arg Arg Arg Lys Thr Thr Thr Arg Arg  
 290 295 300  
 Ser Pro Ser Pro His Arg Arg Cys Asn His Pro Cys Arg Pro Gly Ala  
 305 310 315 320  
 Glu Ser Val Pro Pro Arg Pro Arg Thr Ser Asp Pro Ala Ala Arg Ala  
 325 330 335  
 Leu Pro Pro Glu His Arg His Leu Asn Phe Arg Gln Leu Cys Arg Ser  
 340 345 350  
 Met Ala Leu Thr  
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 20 25 30

Phe Met Gly Thr Trp Ser Asp Ile Gly Thr Ser Gln Leu Asn Gly Gly  
           35                                  40                                  45  
 Ala Phe Asn Trp Ser Ser Leu Trp Ser Gly Leu Lys Asn Phe Gly Ser  
           50                                  55                                  60  
 Thr Leu Lys Thr Tyr Gly Ser Lys Ala Trp Asn Ser Thr Thr Gly Gln  
   65                                  70                                  75                                  80  
 Ala Leu Arg Asp Lys Leu Lys Glu Gln Asn Phe Gln Gln Lys Val Val  
                                   85                                  90                                  95  
 Asp Gly Leu Ala Ser Gly Ile Asn Gly Val Val Asp Leu Ala Asn Gln  
                                   100                                  105                                  110  
 Ala Val Gln Arg Gln Ile Asn Ser Arg Leu Asp Pro Val Pro Pro Ala  
                                   115                                  120                                  125  
 Gly Ser Val Glu Met Pro Gln Val Glu Glu Glu Leu Pro Pro Leu Asp  
   130                                  135                                  140  
 Lys Arg Gly Glu Lys Arg Pro Arg Pro Asp Ala Glu Glu Thr Leu Leu  
   145                                  150                                  155                                  160  
 Thr His Thr Asp Glu Pro Pro Pro Tyr Glu Glu Ala Val Lys Leu Gly  
                                   165                                  170                                  175  
 Leu Pro Thr Thr Arg Pro Ile Ala Pro Leu Ala Thr Gly Val Leu Lys  
                                   180                                  185                                  190  
 Pro Glu Lys Pro Ala Thr Leu Asp Leu Xaa Pro Pro Gln Pro Ser Arg  
                                   195                                  200                                  205  
 Pro Xaa Thr Val Ala Lys Pro Leu Pro Pro Val Ala Val Ala Arg Ala  
   210                                  215                                  220  
 Arg Pro Gly Gly Thr Ala Arg Pro His Ala Asn Trp Gln Ser Thr Leu  
   225                                  230                                  235                                  240  
 Asn Ser Ile Val Gly Leu Gly Val Gln Ser Val Lys Arg Arg Arg Xaa  
                                   245                                  250                                  255

Tyr

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Gly Gln Asp Ala Ser Glu Tyr Leu Ser Pro Gly Leu Val Gln Phe Ala
20     25     30

Arg Ala Thr Asp Thr Tyr Phe Ser Leu Gly Asn Lys Phe Arg Asn Pro
35     40     45

Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu
50     55     60

Thr Leu Arg Phe Val Pro Val Asp Arg Glu Asp Asn Thr Tyr Ser Tyr
65     70     75     80

Lys Val Arg Tyr Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met
85     90     95

Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Ser
100    105    110

Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ser Leu Ala Pro Lys Gly
115    120    125

Ala Pro Asn Thr Cys Gln Trp Thr Tyr Lys Ala Asp Gly Glu Thr Ala
130    135    140

Thr Glu Lys Thr Tyr Thr Tyr Gly Asn Ala Pro Val Gln Gly Ile Asn
145    150    155    160

Ile Thr Lys Asp Gly Ile Gln Leu Gly Thr Asp Thr Asp Asp Gln Pro
165    170    175

Ile Tyr Ala Asp Lys Thr Tyr Gln Pro Glu Pro Gln Val Gly Asp Ala
180    185    190

Glu Trp His Asp Ile Thr Gly Thr Asp Glu Lys Tyr Gly Gly Arg Ala
195    200    205

Leu Lys Pro Asp Thr Lys Met Lys Pro Cys Tyr Gly Ser Phe Ala Lys
210    215    220

Pro Thr Asn Lys Glu Gly Gly Gln Ala Asn Val Lys Thr Gly Thr Gly
225    230    235    240

Thr Thr Lys Glu Tyr Asp Ile Asp Met Ala Phe Phe Asp Asn Arg Ser
245    250    255

Ala Ala Ala Ala Gly Leu Ala Pro Glu Ile Val Leu Tyr Thr Glu Asn
260    265    270

Val Asp Leu Glu Thr Pro Asp Thr His Ile Val Tyr Lys Ala Gly Thr
275    280    285

Asp Asp Ser Ser Ser Ser Ile Asn Leu Gly Gln Gln Ala Met Pro Asn
290    295    300

Arg Pro Asn Tyr Ile Gly Phe Arg Asp Asn Phe Ile Gly Leu Met Tyr
305    310    315    320

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Tyr Asn Ser Thr Gly Asn Met Gly Val Leu Ala Gly Gln Ala Ser Gln  
 325 330 335  
 Leu Asn Ala Val Val Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser Tyr  
 340 345 350  
 Gln Leu Leu Leu Asp Ser Leu Gly Asp Arg Thr Arg Tyr Phe Ser Met  
 355 360 365  
 Trp Asn Gln Ala Val Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile Glu  
 370 375 380  
 Asn His Gly Val Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu Asp  
 385 390 395 400  
 Ala Val Gly Arg Thr Asp Thr Tyr Gln Gly Ile Lys Ala Asn Gly Thr  
 405 410 415  
 Asp Gln Thr Thr Trp Thr Lys Asp Asp Ser Val Asn Asp Ala Asn Glu  
 420 425 430  
 Ile Gly Lys Gly Asn Pro Phe Ala Met Glu Ile Asn Ile Gln Ala Asn  
 435 440 445  
 Leu Trp Arg Asn Phe Leu Tyr Ala Asn Val Ala Leu Tyr Leu Pro Asp  
 450 455 460  
 Ser Tyr Lys Tyr Thr Pro Ala Asn Val Thr Leu Pro Thr Asn Thr Asn  
 465 470 475 480  
 Thr Tyr Asp Tyr Met Asn Gly Arg Val Val Ala Pro Ser Leu Val Asp  
 485 490 495  
 Ser Tyr Ile Asn Ile Gly Ala Arg Trp Ser Leu Asp Pro Met Asp Asn  
 500 505 510  
 Val Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg Tyr Arg Ser  
 515 520 525  
 Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile Gln Val Pro  
 530 535 540  
 Gln Lys Phe Phe Ala Ile Lys Ser Leu Leu Leu Leu Pro Gly Ser Tyr  
 545 550 555 560  
 Thr Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn Met Ile Leu Gln Ser  
 565 570 575  
 Ser Leu Gly Asn Asp Leu Arg Thr Asp Gly Ala Ser Ile Ser Phe Thr  
 580 585 590  
 Ser Ile Asn Leu Tyr Ala Thr Phe Phe Pro Met Ala His Asn Thr Ala  
 595 600 605  
 Ser Thr Leu Glu Ala Met Leu Arg Asn Asp Thr Asn Asp Gln Ser Phe  
 610 615 620  
 Asn Asp Tyr Leu Ser Ala Ala Asn Met Leu Tyr Pro Ile Pro Ala Asn  
 625 630 635 640  
 Ala Thr Asn Val Pro Ile Ser Ile Pro Ser Arg Asn Trp Ala Ala Phe  
 645 650 655

Arg Gly Trp Ser Phe Thr Arg Leu Lys Thr Lys Glu Thr Pro Ser Leu  
 660 665 670  
 Gly Ser Gly Phe Asp Pro Tyr Phe Val Tyr Ser Gly Ser Ile Pro Tyr  
 675 680 685  
 Leu Asp Gly Thr Phe Tyr Leu Asn His Thr Phe Lys Lys Val Ser Ile  
 690 695 700  
 Thr Phe Asp Ser Ser Val Ser Trp Pro Gly Asn Asp Arg Leu Leu Thr  
 705 710 715 720  
 Pro Asn Glu Phe Glu Ile Lys Arg Thr Val Asp Gly Glu Gly Tyr Asn  
 725 730 735  
 Val Ala Gln Cys Asn Met Thr Lys Asp Trp Phe Leu Val Gln Met Leu  
 740 745 750  
 Ala His Tyr Asn Ile Gly Tyr Gln Gly Phe Tyr Val Pro Glu Gly Tyr  
 755 760 765  
 Lys Asp Arg Met Tyr Ser Phe Phe Arg Asn Phe Gln Pro Met Ser Arg  
 770 775 780  
 Gln Val Val Asp Glu Val Asn Tyr Lys Asp Tyr Gln Ala Val Thr Leu  
 785 790 795 800  
 Ala Tyr Gln His Asn Asn Ser Gly Phe Val Gly Tyr Leu Ala Pro Thr  
 805 810 815  
 Met Arg Gln Gly Gln Pro Tyr Pro Ala Xaa Tyr Pro Tyr Pro Leu Ile  
 820 825 830  
 Gly Lys Ser Ala Val Thr Ser Val Thr Gln Lys Lys Phe Leu Cys Asp  
 835 840 845  
 Arg Val Met Trp Arg Ile Pro Phe Ser Ser Asn Phe Met Ser Met Gly  
 850 855 860  
 Ala Leu Thr Asp Leu Gly Gln Asn Met Leu Tyr Ala Asn Ser Ala His  
 865 870 875 880  
 Ala Leu Asp Met Asn Phe Glu Val Asp Pro Met Asp Glu Ser Thr Leu  
 885 890 895  
 Leu Tyr Val Val Phe Glu Val Phe Asp Val Val Arg Val His Gln Pro  
 900 905 910  
 His Arg Gly Val Ile Glu Ala Val Tyr Xaa Arg Thr Pro Phe Ser Ala  
 915 920 925  
 Gly Asn Ala Thr Thr  
 930

&lt;210&gt; 17

&lt;211&gt; 513

&lt;212&gt; PRT

&lt;213&gt; chimpanzee C68 adenovirus protein

<220> <221> MISC\_FEATURE  
 <222> (511)..(511)  
 <223> Xaa can be any amino acid

<400> 17

Met	Ala	Gly	Arg	Gly	Gly	Ser	Gln	Ser	Glu	Arg	Arg	Arg	Glu	Arg	Thr	1	5	10	15
Pro	Glu	Arg	Gly	Arg	Gly	Ser	Ala	Ser	His	Pro	Pro	Ser	Arg	Gly	Gly	20	25	30	
Glu	Ser	Pro	Ser	Pro	Pro	Pro	Leu	Pro	Pro	Lys	Arg	His	Thr	Tyr	Arg	35	40	45	
Arg	Val	Ala	Ser	Asp	Gln	Glu	Glu	Glu	Glu	Ile	Val	Val	Val	Ser	Glu	50	55	60	
Asn	Ser	Arg	Ser	Pro	Ser	Pro	Ser	Pro	Thr	Ser	Pro	Pro	Pro	Leu	Pro	65	70	75	
Pro	Lys	Lys	Lys	Pro	Arg	Lys	Thr	Lys	His	Val	Val	Leu	Gln	Asp	Val	85	90	95	
Ser	Gln	Asp	Ser	Glu	Asp	Glu	Arg	Gln	Ala	Glu	Glu	Glu	Leu	Ala	Ala	100	105	110	
Val	Gly	Phe	Ser	Tyr	Pro	Pro	Val	Arg	Ile	Thr	Glu	Lys	Asp	Gly	Lys	115	120	125	
Arg	Ser	Phe	Glu	Thr	Leu	Asp	Glu	Ser	Asp	Pro	Leu	Ala	Ala	Ala	Ala	130	135	140	
Ser	Ala	Lys	Met	Met	Val	Lys	Asn	Pro	Met	Ser	Leu	Pro	Ile	Val	Ser	145	150	155	
Ala	Trp	Glu	Lys	Gly	Met	Glu	Ile	Met	Thr	Met	Leu	Met	Asp	Arg	Tyr	165	170	175	
Arg	Val	Glu	Thr	Asp	Leu	Lys	Ala	Asn	Phe	Gln	Leu	Met	Pro	Glu	Gln	180	185	190	
Gly	Glu	Val	Tyr	Arg	Arg	Ile	Cys	His	Leu	Tyr	Ile	Asn	Glu	Glu	His	195	200	205	
Arg	Gly	Ile	Pro	Leu	Thr	Phe	Thr	Ser	Asn	Lys	Thr	Leu	Thr	Thr	Met	210	215	220	
Met	Gly	Arg	Phe	Leu	Gln	Gly	Phe	Val	His	Ala	His	Ser	Gln	Ile	Ala	225	230	235	
His	Lys	Asn	Trp	Glu	Cys	Thr	Gly	Cys	Ala	Leu	Trp	Leu	His	Gly	Cys	245	250	255	
Thr	Glu	Ala	Glu	Gly	Lys	Leu	Arg	Cys	Leu	His	Gly	Thr	Thr	Met	Ile	260	265	270	
Gln	Lys	Glu	His	Met	Ile	Glu	Met	Asp	Val	Ala	Ser	Glu	Asn	Gly	Gln	275	280	285	
Arg	Ala	Leu	Lys	Glu	Asn	Pro	Asp	Arg	Ala	Lys	Ile	Thr	Gln	Asn	Arg	290	295	300	

Trp Gly Arg Ser Val Val Gln Leu Ala Asn Asn Asp Ala Arg Cys Cys  
 305 310 315 320  
 Val His Asp Ala Gly Cys Ala Thr Asn Gln Phe Ser Ser Lys Ser Cys  
 325 330 335  
 Gly Val Phe Phe Thr Glu Gly Ala Lys Ala Gln Gln Ala Phe Arg Gln  
 340 345 350  
 Leu Glu Ala Phe Met Lys Ala Met Tyr Pro Gly Met Asn Ala Asp Gln  
 355 360 365  
 Ala Gln Met Met Leu Ile Pro Leu His Cys Asp Cys Asn His Lys Pro  
 370 375 380  
 Gly Cys Val Pro Thr Met Gly Arg Gln Thr Cys Lys Met Thr Pro Phe  
 385 390 395 400  
 Gly Met Ala Asn Ala Glu Asp Leu Asp Val Glu Ser Ile Thr Asp Ala  
 405 410 415  
 Thr Val Leu Ala Ser Val Lys His Pro Ala Leu Met Val Phe Gln Cys  
 420 425 430  
 Cys Asn Pro Val Tyr Arg Asn Ser Arg Ala Gln Asn Ala Gly Pro Asn  
 435 440 445  
 Cys Asp Phe Lys Ile Ser Ala Pro Asp Leu Leu Gly Ala Leu Gln Leu  
 450 455 460  
 Thr Arg Lys Leu Trp Thr Asp Ser Phe Pro Asp Thr Pro Leu Pro Lys  
 465 470 475 480  
 Leu Leu Ile Pro Glu Phe Lys Trp Leu Ala Lys Tyr Gln Phe Arg Asn  
 485 490 495  
 Val Ser Leu Pro Ala Gly His Ala Glu Thr Arg Lys Asn Pro Xaa Asp  
 500 505 510

Phe

<210> 18  
 <211> 222  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 18

Met Pro Arg Gly Asn Lys Lys Leu Lys Val Glu Leu Pro Pro Val Glu  
 1 5 10 15  
 Asp Leu Glu Glu Asp Trp Glu Asn Ser Ser Gln Ala Glu Glu Glu  
 20 25 30  
 Met Glu Glu Asp Trp Asp Ser Thr Gln Ala Glu Glu Asp Ser Leu Gln  
 35 40 45  
 Asp Ser Leu Glu Glu Asp Glu Glu Glu Ala Glu Glu Glu Val Glu Glu  
 50 55 60

Ala Ala Ala Ala Arg Pro Ser Ser Ser Ala Gly Glu Lys Ala Ser Ser  
 65 70 75 80  
 Thr Asp Thr Ile Ser Ala Pro Gly Arg Gly Pro Ala Arg Pro His Ser  
 85 90 95  
 Arg Trp Asp Glu Thr Gly Arg Phe Pro Asn Pro Thr Thr Gln Thr Ala  
 100 105 110  
 Pro Thr Thr Ser Lys Lys Arg Gln Gln Gln Gln Lys Lys Thr Ser Arg  
 115 120 125  
 Lys Pro Ala Ala Arg Lys Ser Thr Ala Ala Ala Ala Gly Gly Leu Arg  
 130 135 140  
 Ile Ala Ala Asn Glu Pro Ala Gln Thr Arg Glu Leu Arg Asn Arg Ile  
 145 150 155 160  
 Phe Pro Thr Leu Tyr Ala Ile Phe Gln Gln Ser Arg Gly Gln Glu Gln  
 165 170 175  
 Glu Leu Lys Val Lys Asn Arg Ser Leu Arg Ser Leu Thr Arg Ser Cys  
 180 185 190  
 Leu Tyr His Lys Ser Glu Asp Gln Leu Gln Arg Thr Leu Glu Asp Ala  
 195 200 205  
 Glu Ala Leu Phe Asn Lys Tyr Cys Ala Leu Thr Leu Lys Glu  
 210 215 220

<210> 19  
 <211> 227  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 19

Met Ser Lys Glu Ile Pro Thr Pro Tyr Met Trp Ser Tyr Gln Pro Gln  
 1 5 10 15  
 Met Gly Leu Ala Ala Gly Ala Ala Gln Asp Tyr Ser Thr Arg Met Asn  
 20 25 30  
 Trp Leu Ser Ala Gly Pro Ala Met Ile Ser Arg Val Asn Asp Ile Arg  
 35 40 45  
 Ala His Arg Asn Gln Ile Leu Leu Glu Gln Ser Ala Leu Thr Ala Thr  
 50 55 60  
 Pro Arg Asn His Leu Asn Pro Arg Asn Trp Pro Ala Ala Leu Val Tyr  
 65 70 75 80  
 Gln Glu Ile Pro Gln Pro Thr Thr Val Leu Leu Pro Arg Asp Ala Gln  
 85 90 95  
 Ala Glu Val Gln Leu Thr Asn Ser Gly Val Gln Leu Ala Gly Gly Ala  
 100 105 110  
 Thr Leu Cys Arg His Arg Pro Ala Gln Gly Ile Lys Arg Leu Val Ile  
 115 120 125

Arg Gly Arg Ser Thr Gln Leu Asn Asp Glu Val Val Ser Ser Ser Leu  
 130 135 140  
 Gly Leu Arg Pro Asp Gly Val Phe Gln Leu Ala Gly Ser Gly Arg Ser  
 145 150 155 160  
 Ser Phe Thr Pro Arg Gln Ala Val Leu Thr Leu Glu Ser Ser Ser Ser  
 165 170 175  
 Gln Pro Arg Ser Gly Gly Ile Gly Thr Leu Gln Phe Val Glu Glu Phe  
 180 185 190  
 Thr Pro Ser Val Tyr Phe Asn Pro Phe Ser Gly Ser Pro Gly His Tyr  
 195 200 205  
 Pro Asp Glu Phe Ile Pro Asn Phe Asp Ala Ile Ser Glu Ser Val Asp  
 210 215 220  
 Gly Tyr Asp  
 225

<210> 20  
 <211> 106  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 20

Met Ser His Gly Gly Ala Ala Asp Leu Ala Arg Leu Arg His Leu Asp  
 1 5 10 15  
 His Cys Arg Arg Phe Arg Cys Phe Ala Arg Asp Leu Ala Glu Phe Ala  
 20 25 30  
 Tyr Phe Glu Leu Pro Glu Glu His Pro Gln Gly Pro Ala His Gly Val  
 35 40 45  
 Arg Ile Val Val Glu Gly Gly Leu Asp Ser His Leu Leu Arg Ile Phe  
 50 55 60  
 Ser Gln Arg Pro Ile Leu Val Glu Arg Glu Gln Gly Gln Thr Leu Leu  
 65 70 75 80  
 Thr Leu Tyr Cys Ile Cys Asn His Pro Gly Leu His Glu Ser Leu Cys  
 85 90 95  
 Cys Leu Leu Cys Thr Glu Tyr Asn Lys Ser  
 100 105

<210> 21  
 <211> 146  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<220> <221> MISC\_FEATURE  
 <222> (62)..(62)  
 <223> Xaa can be any amino acid

&lt;400&gt; 21

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Met Lys Val Phe Val Val Cys Cys Val Leu Ser Ile Ile Lys Ala Glu
1          5          10          15

Thr Ala Thr Thr Pro Asp Phe Arg Val Ser Lys Leu Gln Leu Phe Gln
          20          25          30

Pro Phe Leu Pro Gly Thr Tyr Gln Cys Val Ser Gly Pro Cys His His
          35          40          45

Thr Phe His Leu Ile Pro Asn Thr Thr Ala Ser Leu Pro Xaa Thr Asn
          50          55          60

Asn Gln Thr Asn Leu His Gln Arg His Arg Arg Asp Leu Ser Glu Ser
65          70          75          80

Asn Thr Thr Thr His Thr Gly Gly Glu Leu Arg Gly Gln Pro Thr Ser
          85          90          95

Gly Ile Tyr Tyr Gly Pro Trp Glu Val Val Gly Leu Ile Thr Leu Gly
          100          105          110

Leu Val Ala Gly Gly Leu Leu Val Leu Cys Tyr Leu Tyr Leu Pro Cys
          115          120          125

Cys Ser Tyr Leu Val Val Leu Cys Cys Trp Phe Lys Lys Trp Gly Arg
130          135          140

Ser Pro
145

```

&lt;210&gt; 22

&lt;211&gt; 176

&lt;212&gt; PRT

&lt;213&gt; chimpanzee C68 adenovirus protein

&lt;220&gt;

&lt;221&gt; MISC\_FEATURE

&lt;222&gt; (28)..(28)

&lt;223&gt; Xaa can be any amino acid

&lt;400&gt; 22

```

Met Gly Lys Ile Thr Leu Val Ser Cys Gly Ala Leu Val Ala Val Leu
1          5          10          15

Leu Ser Ile Val Gly Leu Gly Gly Ala Ala Val Xaa Lys Glu Lys Ala
          20          25          30

Asp Pro Cys Leu His Phe Asn Pro Asn Lys Cys Gln Leu Ser Phe Gln
          35          40          45

Pro Asp Gly Asn Arg Cys Ala Val Leu Ile Lys Cys Gly Trp Glu Cys
50          55          60

Glu Asn Val Arg Ile Glu Tyr Asn Asn Lys Thr Arg Asn Asn Thr Leu
65          70          75          80

Ala Ser Val Trp Gln Pro Gly Asp Pro Glu Trp Tyr Thr Val Ser Val
          85          90          95

```



Pro Gly Ala Asp Gly Ser Pro Arg Thr Val Asn Asn Thr Phe Ile Phe  
 100 105 110  
 Ala His Met Cys Asp Thr Val Met Trp Met Ser Lys Gln Tyr Asp Met  
 115 120 125  
 Trp Pro Pro Thr Lys Glu Asn Ile Val Val Phe Ser Ile Ala Tyr Ser  
 130 135 140  
 Leu Cys Thr Ala Leu Ile Thr Ala Ile Val Cys Leu Ser Ile His Met  
 145 150 155 160  
 Leu Ile Ala Ile Arg Pro Arg Asn Asn Ala Glu Lys Glu Lys Gln Pro  
 165 170 175

<210> 23  
 <211> 204  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 23

Met Ala Ser Val Lys Phe Leu Leu Leu Phe Ala Ser Leu Ile Ala Val  
 1 5 10 15  
 Ile His Gly Met Ser Asn Glu Lys Ile Thr Ile Tyr Thr Gly Thr Asn  
 20 25 30  
 His Thr Leu Lys Gly Pro Glu Lys Ala Thr Glu Val Ser Trp Tyr Cys  
 35 40 45  
 Tyr Phe Asn Glu Ser Asp Val Ser Thr Glu Leu Cys Gly Asn Asn Asn  
 50 55 60  
 Lys Lys Asn Glu Ser Ile Thr Leu Ile Lys Phe Gln Cys Gly Ser Asp  
 65 70 75 80  
 Leu Thr Leu Ile Asn Ile Thr Arg Asp Tyr Val Gly Met Tyr Tyr Gly  
 85 90 95  
 Thr Thr Ala Gly Ile Ser Asp Met Glu Phe Tyr Gln Val Ser Val Ser  
 100 105 110  
 Glu Pro Thr Thr Pro Arg Met Thr Thr Thr Thr Lys Thr Thr Pro Val  
 115 120 125  
 Thr Thr Met Gln Leu Thr Thr Asn Asn Ile Phe Ala Met Arg Gln Met  
 130 135 140  
 Val Asn Asn Ser Thr Gln Pro Thr Pro Pro Ser Glu Glu Ile Pro Lys  
 145 150 155 160  
 Ser Met Ile Gly Ile Ile Val Ala Val Val Val Cys Met Leu Ile Ile  
 165 170 175  
 Ala Leu Cys Met Val Tyr Tyr Ala Phe Cys Tyr Arg Lys His Arg Leu  
 180 185 190  
 Asn Asp Lys Leu Glu His Leu Leu Ser Val Glu Phe  
 195 200

<210> 24  
 <211> 91  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 24

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Met Ile Pro Arg Gln Phe Leu Ile Thr Ile Leu Ile Cys Leu Leu Gln
1           5           10           15

Val Cys Ala Thr Leu Ala Leu Val Ala Asn Ala Ser Pro Asp Cys Ile
          20           25           30

Gly Pro Phe Ala Ser Tyr Val Leu Phe Ala Phe Thr Thr Cys Ile Cys
          35           40           45

Cys Cys Ser Ile Val Cys Leu Leu Ile Thr Phe Phe Gln Phe Ile Asp
          50           55           60

Trp Ile Phe Val Arg Ile Ala Tyr Leu Arg His His Pro Gln Tyr Arg
65           70           75           80

Asp Gln Arg Val Ala Arg Leu Leu Arg Leu Leu
          85           90
  
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<210> 25  
 <211> 143  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<220>  
 <221> MISC\_FEATURE  
 <222> (5)..(5)  
 <223> Xaa can be any amino acid

<400> 25

```

Met Arg Ala Val Xaa Leu Leu Ala Leu Leu Leu Val Leu Pro Arg
1           5           10           15

Pro Val Asp Pro Arg Ser Pro Thr Gln Ser Pro Glu Glu Val Arg Lys
          20           25           30

Cys Lys Phe Gln Glu Pro Trp Lys Phe Leu Lys Cys Tyr Arg Gln Lys
          35           40           45

Ser Asp Met His Pro Ser Trp Ile Met Ile Ile Gly Ile Val Asn Ile
          50           55           60

Leu Ala Cys Thr Leu Ile Ser Phe Val Ile Tyr Pro Cys Phe Asp Phe
65           70           75           80

Gly Trp Asn Ser Pro Glu Ala Leu Tyr Leu Pro Pro Glu Pro Asp Thr
          85           90           95

Pro Pro Gln Gln Pro Gln Ala His Ala Leu Pro Pro Leu Gln Pro Arg
          100          105          110

Pro Gln Tyr Met Pro Ile Leu Asp Tyr Glu Ala Glu Pro Gln Arg Pro
          115          120          125
  
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Met Leu Pro Ala Ile Ser Tyr Phe Asn Leu Thr Gly Gly Asp Asp  
 130 135 140

<210> 26  
 <211> 135  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 26

Met Thr Asp Pro Leu Ala Asn Asn Asn Val Asn Asp Leu Leu Leu Asp  
 1 5 10 15

Met Asp Gly Arg Ala Ser Glu Gln Arg Leu Ala Gln Leu Arg Ile Arg  
 20 25 30

Gln Gln Gln Glu Arg Ala Val Lys Glu Leu Gln Asp Ala Val Ala Ile  
 35 40 45

His Gln Cys Lys Arg Gly Ile Phe Cys Leu Val Lys Gln Ala Lys Ile  
 50 55 60

Ser Tyr Glu Val Thr Pro Asn Asp His Arg Leu Ser Tyr Glu Leu Leu  
 65 70 75 80

Gln Gln Arg Gln Lys Phe Thr Cys Leu Val Gly Val Asn Pro Ile Val  
 85 90 95

Ile Thr Gln Gln Ser Gly Asp Thr Lys Gly Cys Ile His Cys Ser Cys  
 100 105 110

Asp Ser Pro Asp Cys Val His Thr Leu Ile Lys Thr Leu Cys Gly Leu  
 115 120 125

Arg Asp Leu Leu Pro Met Asn  
 130 135

<210> 27  
 <211> 425  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 27

Met Ser Lys Lys Arg Val Arg Val Asp Asp Asp Phe Asp Pro Val Tyr  
 1 5 10 15

Pro Tyr Asp Ala Asp Asn Ala Pro Thr Val Pro Phe Ile Asn Pro Pro  
 20 25 30

Phe Val Ser Ser Asp Gly Phe Gln Glu Lys Pro Leu Gly Val Leu Ser  
 35 40 45

Leu Arg Leu Ala Asp Pro Val Thr Thr Lys Asn Gly Glu Ile Thr Leu  
 50 55 60

Lys Leu Gly Glu Gly Val Asp Leu Asp Ser Ser Gly Lys Leu Ile Ser  
 65 70 75 80

Asn Thr Ala Thr Lys Ala Ala Ala Pro Leu Ser Phe Ser Asn Asn Thr  
 85 90 95  
 Ile Ser Leu Asn Met Asp His Pro Phe Tyr Thr Lys Asp Gly Lys Leu  
 100 105 110  
 Ser Leu Gln Val Ser Pro Pro Leu Asn Ile Leu Arg Thr Ser Ile Leu  
 115 120 125  
 Asn Thr Leu Ala Leu Gly Phe Gly Ser Gly Leu Gly Leu Arg Gly Ser  
 130 135 140  
 Ala Leu Ala Val Gln Leu Val Ser Pro Leu Thr Phe Asp Thr Asp Gly  
 145 150 155 160  
 Asn Ile Lys Leu Thr Leu Asp Arg Gly Leu His Val Thr Thr Gly Asp  
 165 170 175  
 Ala Ile Glu Ser Asn Ile Ser Trp Ala Lys Gly Leu Lys Phe Glu Asp  
 180 185 190  
 Gly Ala Ile Ala Thr Asn Ile Gly Asn Gly Leu Glu Phe Gly Ser Ser  
 195 200 205  
 Ser Thr Glu Thr Gly Val Asp Asp Ala Tyr Pro Ile Gln Val Lys Leu  
 210 215 220  
 Gly Ser Gly Leu Ser Phe Asp Ser Thr Gly Ala Ile Met Ala Gly Asn  
 225 230 235 240  
 Lys Glu Asp Asp Lys Leu Thr Leu Trp Thr Thr Pro Asp Pro Ser Pro  
 245 250 255  
 Asn Cys Gln Ile Leu Ala Glu Asn Asp Ala Lys Leu Thr Leu Cys Leu  
 260 265 270  
 Thr Lys Cys Gly Ser Gln Ile Leu Ala Thr Val Ser Val Leu Val Val  
 275 280 285  
 Gly Ser Gly Asn Leu Asn Pro Ile Thr Gly Thr Val Ser Ser Ala Gln  
 290 295 300  
 Val Phe Leu Arg Phe Asp Ala Asn Gly Val Leu Leu Thr Glu His Ser  
 305 310 315 320  
 Thr Leu Lys Lys Tyr Trp Gly Tyr Arg Gln Gly Asp Ser Ile Asp Gly  
 325 330 335  
 Thr Pro Tyr Thr Asn Ala Val Gly Phe Met Pro Asn Leu Lys Ala Tyr  
 340 345 350  
 Pro Lys Ser Gln Ser Ser Thr Thr Lys Asn Asn Ile Val Gly Gln Val  
 355 360 365  
 Tyr Met Asn Gly Asp Val Ser Lys Pro Met Leu Leu Thr Ile Thr Leu  
 370 375 380  
 Asn Gly Thr Asp Asp Ser Asn Ser Thr Tyr Ser Met Ser Phe Ser Tyr  
 385 390 395 400  
 Thr Trp Thr Asn Gly Ser Tyr Val Gly Ala Thr Phe Gly Ala Asn Ser  
 405 410 415

Tyr Thr Phe Ser Tyr Ile Ala Gln Glu  
                     420                    425

<210> 28  
 <211> 83  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 28

Ile Thr Val Ile Pro Thr Thr Glu Asp Asn Pro Gln Leu Leu Ser Cys  
 1                    5                    10                    15  
 Glu Val Gln Met Arg Glu Cys Pro Glu Gly Phe Ile Ser Leu Thr Asp  
                     20                    25                    30  
 Pro Arg Leu Ala Arg Ser Glu Thr Val Trp Asn Val Glu Thr Lys Ser  
                     35                    40                    45  
 Met Ser Ile Thr Asn Gly Ile Gln Met Phe Lys Ala Val Arg Gly Glu  
                     50                    55                    60  
 Arg Val Val Tyr Ser Met Ser Trp Glu Gly Gly Gly Lys Ile Thr Ala  
 65                    70                    75                    80  
 Arg Ile Leu

<210> 29  
 <211> 301  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 29

Met Ser Glu Ser Asn Cys Ile Met Thr Arg Ser Arg Thr Arg Ser Ala  
 1                    5                    10                    15  
 Ala Ser Arg His His Pro Tyr Arg Pro Ala Pro Leu Pro Arg Cys Glu  
                     20                    25                    30  
 Glu Thr Glu Thr Arg Ala Ser Leu Val Glu Asp His Pro Val Leu Pro  
                     35                    40                    45  
 Asp Cys Asp Thr Leu Ser Met His Asn Val Ser Ser Val Arg Gly Leu  
                     50                    55                    60  
 Pro Cys Ser Ala Gly Phe Ala Val Leu Gln Glu Phe Pro Val Pro Trp  
 65                    70                    75                    80  
 Asp Met Val Leu Thr Pro Glu Glu Leu Arg Val Leu Lys Arg Cys Met  
                     85                    90                    95  
 Ser Ile Cys Leu Cys Cys Ala Asn Ile Asp Leu Phe Ser Ser Gln Met  
                     100                    105                    110  
 Ile His Gly Tyr Glu Arg Trp Val Leu His Cys His Cys Arg Asp Pro  
                     115                    120                    125  
 Gly Ser Leu Arg Cys Met Ala Gly Gly Ala Val Leu Ala Leu Trp Phe  
                     130                    135                    140

Arg Arg Ile Ile Arg Gly Cys Met Phe Asn Gln Arg Val Met Trp Tyr  
 145 150 155 160  
 Arg Glu Val Val Asn Arg His Met Pro Lys Glu Ile Met Tyr Val Gly  
 165 170 175  
 Ser Val Phe Trp Arg Gly His His Leu Ile Tyr Leu Arg Ile Trp Tyr  
 180 185 190  
 Asp Gly His Val Gly Ser Ile Leu Pro Ala Met Ser Phe Gly Trp Ser  
 195 200 205  
 Val Leu Asn Tyr Gly Leu Leu Asn Asn Leu Val Val Leu Cys Cys Thr  
 210 215 220  
 Tyr Cys Ser Asp Leu Ser Glu Ile Arg Met Arg Cys Cys Ala Arg Arg  
 225 230 235 240  
 Thr Arg Arg Leu Met Leu Arg Ala Val Gly Ile Met Leu Arg Glu Ser  
 245 250 255  
 Leu Asp Pro Asp Pro Leu Ser Ser Ser Leu Thr Glu Arg Arg Arg Gln  
 260 265 270  
 Arg Leu Leu Arg Gly Leu Met Arg His His Arg Pro Ile Pro Phe Ala  
 275 280 285  
 Asp Tyr Asp Ser His Arg Arg Ser Ser Ala Ser Ser Arg  
 290 295 300

<210> 30  
 <211> 121  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 30

Met Val Leu Pro Val Leu Pro Ser Pro Ala Val Thr Glu Thr Gln Gln  
 1 5 10 15  
 Asn Cys Ile Ile Trp Leu Gly Leu Ala His Ser Thr Val Val Asp Val  
 20 25 30  
 Ile Arg Ala Ile Arg His Asp Gly Ile Phe Ile Thr Pro Glu Ala Leu  
 35 40 45  
 Asp Leu Leu His Gly Leu Arg Glu Trp Leu Phe Tyr Asn Phe Asn Thr  
 50 55 60  
 Glu Arg Ser Lys Arg Arg Asp Arg Arg Arg Arg Ser Val Cys Ser Ala  
 65 70 75 80  
 Arg Thr Arg Phe Cys Tyr Ser Lys Tyr Glu Asn Val Arg Lys Gln Leu  
 85 90 95  
 His His Asp Thr Val Ala Asn Thr Ile Ser Arg Val Pro Pro Ser Pro  
 100 105 110  
 Val Ser Ala Gly Pro Leu Thr Thr Leu  
 115 120

<210> 31  
 <211> 117  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<220> <221> MISC\_FEATURE  
 <222> (45)..(45)  
 <223> Xaa can be any amino acid

<400> 31

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Met Arg Val Cys Leu Arg Met Pro Val Glu Gly Ala Leu Arg Glu Leu
1           5           10           15

Phe Ile Met Ala Gly Leu Asp Leu Pro His Glu Leu Val Arg Ile Ile
          20           25           30

Gln Gly Trp Lys Asn Glu Asn Tyr Leu Gly Met Val Xaa Glu Cys Asn
          35           40           45

Met Met Ile Glu Glu Leu Glu Asn Pro Pro Ala Phe Ala Ile Val Leu
 50           55           60

Phe Leu Asp Val Arg Val Glu Ala Leu Leu Glu Ala Thr Val Glu His
65           70           75           80

Leu Glu Asn Arg Ile Thr Phe Asp Leu Ala Val Ile Phe His Gln His
          85           90           95

Ser Gly Gly Glu Arg Cys His Leu Arg Asp Leu His Phe Glu Val Leu
          100          105          110

Arg Asp Arg Leu Asp
          115

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<210> 32  
 <211> 129  
 <212> PRT  
 <213> chimpanzee C68 adenovirus protein

<400> 32

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Met Leu Glu Arg Thr Ala Cys Ile Tyr Phe Ile Val Val Pro Glu Ala
1           5           10           15

Leu Asn Val His Leu Glu Asp Phe Ser Phe Val Asp Phe Leu Lys Asn
          20           25           30

Cys Leu Gly Asp Phe Leu Ser Ser Tyr Leu Glu Asp Ile Thr Gly Ser
          35           40           45

Ser Gln His Ala Tyr Ser Ser Leu Ala Phe Gly Asn Ala His Trp Gly
 50           55           60

Gly Leu Arg Phe Ile Cys Thr Val Ala Cys Pro Asn Leu Ile Pro Gly
65           70           75           80

Gly Pro Met Ala Lys Asn Phe Gly Glu Asp Met Lys Glu Tyr Leu Gln
          85           90           95

```

Leu Leu Leu Arg Glu Glu Leu Arg Asp Arg Gly Arg Asp Phe Asp Ile  
 100 105 110

Pro Leu Val Asn Leu Leu Gln Val Asn Gln Glu Gln Asn Ile Leu Glu  
 115 120 125

Leu

<210> 33  
 <211> 36521  
 <212> DNA  
 <213> chimpanzee C68 adenovirus

<220>  
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 <222> (8268)..(8268)  
 <223> can be a or c or g or t

<220>  
 <221> misc\_feature  
 <222> (8322)..(8322)  
 <223> can be a or c or g or t

<220>  
 <221> misc\_feature  
 <222> (8535)..(8535)  
 <223> can be a or c or g or t

<220>  
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 <222> (16753)..(16753)  
 <223> can be a or c or g or t

<220>  
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 <222> (28095)..(28095)  
 <223> can be a or c or g or t

<220>  
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 <222> (29373)..(29373)  
 <223> can be a or c or g or t

<220>  
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 <222> (30447)..(30447)  
 <223> can be a or c or g or t

<220>  
 <221> misc\_feature  
 <222> (31015)..(31015)  
 <223> can be a or c or g or t

<400> 33  
 ccttcttcaa taatatacct tcaaactttt tgtgcgcggtt aatatgcaaa tgaggcggtt 60  
 gaatttgggg aggaagggcg gtgattggtc gagggatgag cgaccgtag gggcggggag 120  
 agtgacgttt tgatgacgtg gttgagagga ggagccagtt tgcaagttct cgtgggaaaa 180  
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 Leu Pro Ile Gly Ile Asp Ser Thr Ser Gly Thr Asp Thr Val Ile Tyr  
 35 40 45  
 Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Val Gly Asn Ala Ser Trp  
 50 55 60  
 Val Asp Ala Asn Gly Thr Glu Glu Lys Tyr Gly Gly Arg Ala Leu Lys  
 65 70 75 80

Asp Thr Thr Lys Met Lys Pro Cys Tyr Gly Ser Phe Ala Lys Pro Thr  
 85 90 95  
 Asn Lys Glu Gly Gly Gln Ala Asn Leu Lys Asp Ser Glu Thr Ala Ala  
 100 105 110  
 Thr Thr Pro Asn Tyr Asp Ile Asp Leu Ala Phe Phe Asp Asn Lys Asn  
 115 120 125  
 Ile Ala Ala Asn Tyr Asp Pro Asp Ile Val Met Tyr Thr Glu Asn Val  
 130 135 140  
 Asp Leu Gln Thr Pro Asp Thr His Ile Val Tyr Lys Pro Gly Thr Glu  
 145 150 155 160  
 Asp Thr Ser Ser Glu Ser Asn Leu Gly Gln Gln Ala Met Pro Asn Arg  
 165 170 175  
 Pro Asn Tyr Ile Gly Phe Arg Asp Asn Phe Ile Gly Leu Met Tyr Tyr  
 180 185 190  
 Asn Ser Thr Gly Asn Met Gly Val Leu Ala Gly Gln Ala Ser Gln Leu  
 195 200 205  
 Asn Ala Val Val Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser Tyr Gln  
 210 215 220  
 Leu Leu Leu Asp Ser Leu Gly Asp Arg Thr Arg Tyr Phe Ser Met Trp  
 225 230 235 240  
 Asn Gln Ala Val Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile Glu Asn  
 245 250 255  
 His Gly Val Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu Asn Gly  
 260 265 270  
 Val Gly Phe Thr Asp Thr Tyr Gln Gly Val Lys Val Lys Thr Asp Ala  
 275 280 285  
 Val Ala Gly Thr Ser Gly Thr Gln Trp Asp Lys Asp Asp Thr Thr Val  
 290 295 300  
 Ser Thr Ala Asn Glu Ile His Gly Gly Asn Pro Phe Ala Met  
 305 310 315

&lt;210&gt; 36

&lt;211&gt; 323

&lt;212&gt; PRT

&lt;213&gt; Human adenovirus type 3

&lt;400&gt; 36

Asn Thr Ser Gln Trp Ile Val Thr Thr Asn Gly Asp Asn Ala Val Thr  
 1 5 10 15  
 Thr Thr Thr Asn Thr Phe Gly Ile Ala Ser Met Lys Gly Gly Asn Ile  
 20 25 30  
 Thr Lys Glu Gly Leu Gln Ile Gly Lys Asp Ile Thr Thr Thr Glu Gly  
 35 40 45

Glu Glu Lys Pro Ile Tyr Ala Asp Lys Thr Tyr Gln Pro Glu Pro Gln  
 50 55 60  
 Val Gly Glu Glu Ser Trp Thr Asp Thr Asp Gly Thr Asn Glu Lys Phe  
 65 70 75 80  
 Gly Gly Arg Ala Leu Lys Pro Ala Thr Asn Met Lys Pro Cys Tyr Gly  
 85 90 95  
 Ser Phe Ala Arg Pro Thr Asn Ile Lys Gly Gly Gln Ala Lys Asn Arg  
 100 105 110  
 Lys Val Lys Pro Thr Thr Glu Gly Gly Val Glu Thr Glu Glu Pro Asp  
 115 120 125  
 Ile Asp Met Glu Phe Phe Asp Gly Arg Asp Ala Val Ala Gly Ala Leu  
 130 135 140  
 Ala Pro Glu Ile Val Leu Tyr Thr Glu Asn Val Asn Leu Glu Thr Pro  
 145 150 155 160  
 Asp Ser His Val Val Tyr Lys Pro Glu Thr Ser Asn Asn Ser His Ala  
 165 170 175  
 Asn Leu Gly Gln Gln Ala Met Pro Asn Arg Pro Asn Tyr Ile Gly Phe  
 180 185 190  
 Arg Asp Asn Phe Val Gly Leu Met Tyr Tyr Asn Ser Thr Gly Asn Met  
 195 200 205  
 Gly Val Leu Ala Gly Gln Ala Ser Gln Leu Asn Ala Val Val Asp Leu  
 210 215 220  
 Gln Asp Arg Asn Thr Glu Leu Ser Tyr Gln Leu Leu Leu Asp Ser Leu  
 225 230 235 240  
 Gly Asp Arg Thr Arg Tyr Phe Ser Met Trp Asn Gln Ala Val Asp Ser  
 245 250 255  
 Tyr Asp Pro Asp Val Arg Ile Ile Glu Asn His Gly Ile Glu Asp Glu  
 260 265 270  
 Leu Pro Asn Tyr Cys Phe Pro Leu Asn Gly Ile Gly Pro Gly His Thr  
 275 280 285  
 Tyr Gln Gly Ile Lys Lys Val Lys Thr Asp Asp Thr Asn Gly Trp Glu  
 290 295 300  
 Lys Asp Ala Asn Val Ala Pro Ala Asn Glu Ile Thr Ile Gly Asn Asn  
 305 310 315 320  
 Leu Ala Met

<210> 37  
 <211> 315  
 <212> PRT  
 <213> Human adenovirus type 7

&lt;400&gt; 37

Asn Thr Ser Gln Trp Ile Val Thr Ala Gly Glu Glu Arg Ala Val Thr  
 1 5 10 15  
 Thr Thr Thr Asn Thr Phe Gly Ile Ala Ser Met Lys Gly Asp Asn Ile  
 20 25 30  
 Thr Lys Glu Gly Leu Glu Ile Gly Lys Asp Ile Thr Ala Asp Asn Lys  
 35 40 45  
 Pro Ile Tyr Ala Asp Lys Thr Tyr Gln Pro Glu Pro Gln Val Gly Glu  
 50 55 60  
 Glu Ser Trp Thr Asp Thr Asp Gly Thr Asn Glu Lys Phe Gly Gly Arg  
 65 70 75 80  
 Ala Leu Lys Pro Ala Thr Lys Met Lys Pro Cys Tyr Gly Ser Phe Ala  
 85 90 95  
 Arg Pro Thr Asn Ile Lys Gly Gly Gln Ala Lys Asn Arg Lys Val Lys  
 100 105 110  
 Pro Thr Glu Gly Asp Val Glu Thr Glu Glu Pro Asp Ile Asp Met Glu  
 115 120 125  
 Phe Phe Asp Gly Arg Glu Ala Ala Asp Ala Phe Ser Pro Glu Ile Val  
 130 135 140  
 Leu Tyr Thr Glu Asn Val Asn Leu Glu Thr Pro Asp Ser His Val Val  
 145 150 155 160  
 Tyr Lys Pro Gly Thr Ser Asp Asp Asn Ser His Ala Asn Leu Gly Gln  
 165 170 175  
 Gln Ala Met Pro Asn Arg Pro Asn Tyr Ile Gly Phe Arg Asp Asn Phe  
 180 185 190  
 Val Gly Leu Met Tyr Tyr Asn Ser Thr Gly Asn Met Gly Val Leu Ala  
 195 200 205  
 Gly Gln Ala Ser Gln Leu Asn Ala Val Val Asp Leu Gln Asp Arg Asn  
 210 215 220  
 Thr Glu Leu Ser Tyr Gln Leu Leu Leu Asp Ser Leu Gly Asp Arg Thr  
 225 230 235 240  
 Arg Tyr Phe Ser Met Trp Asn Gln Ala Val Asp Ser Tyr Asp Pro Asp  
 245 250 255  
 Val Arg Ile Ile Glu Asn His Gly Ile Glu Asp Glu Leu Pro Asn Tyr  
 260 265 270  
 Cys Phe Pro Leu Asp Gly Ile Gly Pro Ala Lys Thr Tyr Gln Gly Ile  
 275 280 285  
 Lys Ser Lys Asp Asn Gly Trp Glu Lys Asp Asp Asn Val Ser Lys Ser  
 290 295 300  
 Asn Glu Ile Ala Ile Gly Asn Asn Gln Ala Met  
 305 310 315



<210> 38  
 <211> 345  
 <212> PRT  
 <213> Human adenovirus type 2

<400> 38

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Asn Ser Cys Glu Trp Glu Gln Thr Glu Asp Ser Gly Arg Ala Val Ala
1      5      10      15
Glu Asp Glu Glu Glu Glu Asp Glu Asp Glu Glu Glu Glu Glu Glu
20      25      30
Gln Asn Ala Arg Asp Gln Ala Thr Lys Lys Thr His Val Tyr Ala Gln
35      40      45
Ala Pro Leu Ser Gly Glu Thr Leu Thr Lys Ser Gly Leu Gln Ile Gly
50      55      60
Ser Lys Asn Ala Glu Thr Gln Ala Lys Pro Val Tyr Ala Asp Pro Ser
65      70      75      80
Tyr Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp Asn Glu Ala Asp
85      90      95
Ala Asn Ala Ala Gly Gly Arg Val Leu Lys Lys Thr Thr Pro Met Lys
100     105     110
Pro Tyr Gly Ser Tyr Ala Arg Pro Thr Asn Pro Phe Gly Gly Gln Ser
115     120     125
Val Leu Val Pro Asp Glu Lys Gly Val Pro Leu Pro Lys Val Asp Leu
130     135     140
Gln Phe Phe Ser Asn Thr Thr Ser Leu Asn Asp Arg Gln Gly Asn Ala
145     150     155     160
Thr Lys Pro Lys Val Val Leu Tyr Ser Glu Asp Val Asn Met Glu Thr
165     170     175
Pro Asp Thr His Leu Ser Tyr Lys Pro Gly Lys Gly Asp Glu Asn Ser
180     185     190
Lys Ala Met Leu Gly Gln Gln Ser Met Pro Asn Arg Pro Asn Tyr Ile
195     200     205
Ala Phe Arg Asp Asn Phe Ile Gly Leu Met Tyr Tyr Asn Ser Thr Gly
210     215     220
Asn Met Gly Val Leu Ala Gly Gln Ala Ser Gln Leu Asn Ala Val Val
225     230     235     240
Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser Tyr Gln Leu Leu Leu Asp
245     250     255
Ser Ile Gly Asp Arg Thr Arg Tyr Phe Ser Met Trp Asn Gln Ala Val
260     265     270
Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile Glu Asn His Gly Thr Glu
275     280     285

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Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu Gly Gly Ile Gly Val Thr  
 290 295 300  
 Asp Thr Tyr Gln Ala Ile Lys Ala Asn Gly Asn Gly Ser Gly Asp Asn  
 305 310 315 320  
 Gly Asp Thr Thr Trp Thr Lys Asp Glu Thr Phe Ala Thr Arg Asn Glu  
 325 330 335  
 Ile Gly Val Gly Asn Asn Phe Ala Met  
 340 345

<210> 39  
 <211> 183  
 <212> PRT  
 <213> human adenovirus protein

<400> 39

Thr Leu Trp Thr Thr Pro Asp Pro Ser Pro Asn Cys Arg Ile His Ser  
 1 5 10 15  
 Asp Asn Asp Cys Lys Phe Thr Leu Val Leu Thr Lys Cys Gly Ser Gln  
 20 25 30  
 Val Leu Ala Thr Val Ala Ala Leu Ala Val Ser Gly Asp Leu Ser Ser  
 35 40 45  
 Met Thr Gly Thr Val Ala Ser Val Ser Ile Phe Leu Arg Phe Asp Gln  
 50 55 60  
 Asn Gly Val Leu Met Glu Asn Ser Ser Leu Lys Lys His Tyr Trp Asn  
 65 70 75 80  
 Phe Arg Asn Gly Asn Ser Thr Asn Ala Asn Pro Tyr Thr Asn Ala Val  
 85 90 95  
 Gly Phe Met Pro Asn Leu Leu Ala Tyr Pro Lys Thr Gln Ser Gln Thr  
 100 105 110  
 Ala Lys Asn Asn Ile Val Ser Gln Val Tyr Leu His Gly Asp Lys Thr  
 115 120 125  
 Lys Pro Met Ile Leu Thr Ile Thr Leu Asn Gly Thr Ser Glu Ser Thr  
 130 135 140  
 Glu Thr Ser Glu Val Ser Thr Tyr Ser Met Ser Phe Thr Trp Ser Trp  
 145 150 155 160  
 Glu Ser Gly Lys Tyr Thr Thr Glu Thr Phe Ala Thr Asn Ser Tyr Thr  
 165 170 175  
 Phe Ser Tyr Ile Ala Gln Glu  
 180

<210> 40  
 <211> 182  
 <212> PRT  
 <213> human adenovirus protein

&lt;400&gt; 40

Thr Leu Trp Thr Thr Pro Ala Pro Ser Pro Asn Cys Arg Leu Asn Ala  
 1 5 10 15  
 Glu Lys Asp Ala Lys Leu Thr Leu Val Leu Thr Lys Cys Gly Ser Gln  
 20 25 30  
 Ile Leu Ala Thr Val Ser Val Leu Ala Val Lys Gly Ser Leu Ala Pro  
 35 40 45  
 Ile Ser Gly Thr Val Gln Ser Ala His Leu Ile Ile Arg Phe Asp Glu  
 50 55 60  
 Asn Gly Val Leu Leu Asn Asn Ser Phe Leu Asp Pro Glu Tyr Trp Asn  
 65 70 75 80  
 Phe Arg Asn Gly Asp Leu Thr Glu Gly Thr Ala Tyr Thr Asn Ala Val  
 85 90 95  
 Gly Phe Met Pro Asn Leu Ser Ala Tyr Pro Lys Ser His Gly Lys Thr  
 100 105 110  
 Ala Lys Ser Asn Ile Val Ser Gln Val Tyr Leu Asn Gly Asp Lys Thr  
 115 120 125  
 Lys Pro Val Thr Leu Thr Ile Thr Leu Asn Gly Thr Gln Glu Thr Gly  
 130 135 140  
 Asp Thr Thr Pro Ser Ala Tyr Ser Met Ser Phe Ser Trp Asp Trp Ser  
 145 150 155 160  
 Gly His Asn Tyr Ile Asn Glu Ile Phe Ala Thr Ser Ser Tyr Thr Phe  
 165 170 175  
 Ser Tyr Ile Ala Gln Glu  
 180

&lt;210&gt; 41

&lt;211&gt; 338

&lt;212&gt; PRT

&lt;213&gt; human adenovirus protein

&lt;400&gt; 41

Ala Pro Lys Gly Ala Pro Asn Pro Cys Glu Trp Asp Glu Ala Ala Thr  
 1 5 10 15  
 Ala Leu Glu Ile Asn Leu Glu Glu Glu Asp Asp Asp Asn Glu Asp Glu  
 20 25 30  
 Val Asp Glu Gln Ala Glu Gln Gln Lys Thr His Val Phe Gly Gln Ala  
 35 40 45  
 Pro Tyr Ser Gly Ile Asn Ile Thr Lys Glu Gly Ile Gln Ile Gly Val  
 50 55 60  
 Glu Gly Gln Thr Pro Lys Tyr Ala Asp Lys Thr Phe Gln Pro Glu Pro  
 65 70 75 80

Gln Ile Gly Glu Ser Gln<sup>7</sup> Trp Tyr Glu Thr Glu Ile Asn His Ala Ala  
 85 90 95  
 Gly Arg Val Leu Lys Lys Thr Thr Pro Met Lys Pro Cys Tyr Gly Ser  
 100 105 110  
 Tyr Ala Lys Pro Thr Asn Glu Asn Gly Gly Gln Gly Ile Leu Val Lys  
 115 120 125  
 Gln Gln Asn Gly Lys Leu Glu Ser Gln Val Glu Met Gln Phe Phe Ser  
 130 135 140  
 Thr Thr Glu Ala Thr Ala Gly Asn Gly Asp Asn Leu Thr Pro Lys Val  
 145 150 155 160  
 Val Leu Tyr Ser Glu Asp Val Asp Ile Glu Thr Pro Asp Thr His Ile  
 165 170 175  
 Ser Tyr Met Pro Thr Ile Lys Glu Gly Asn Ser Arg Glu Leu Met Gly  
 180 185 190  
 Gln Gln Ser Met Pro Asn Arg Pro Asn Tyr Ile Ala Phe Arg Asp Asn  
 195 200 205  
 Phe Ile Gly Leu Met Tyr Tyr Asn Ser Thr Gly Asn Met Gly Val Leu  
 210 215 220  
 Ala Gly Gln Ala Ser Gln Leu Asn Ala Val Val Asp Leu Gln Asp Arg  
 225 230 235 240  
 Asn Thr Glu Leu Ser Tyr Gln Leu Leu Leu Asp Ser Ile Gly Asp Arg  
 245 250 255  
 Thr Arg Tyr Phe Ser Met Trp Asn Gln Ala Val Asp Ser Tyr Asp Pro  
 260 265 270  
 Asp Val Arg Ile Ile Glu Asn His Gly Thr Glu Asp Glu Leu Pro Asn  
 275 280 285  
 Tyr Cys Phe Pro Leu Gly Gly Val Ile Asn Thr Glu Thr Leu Thr Lys  
 290 295 300  
 Val Lys Pro Lys Thr Gly Gln Glu Asn Gly Trp Glu Lys Asp Ala Thr  
 305 310 315 320  
 Glu Phe Ser Asp Lys Asn Glu Ile Arg Val Gly Asn Asn Phe Ala Met  
 325 330 335  
 Glu Ile